Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 27th, 2014 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER
   a. Roll Call & Introductions R. Citron (OSU)
   b. Conflict of Interest Declaration R. Citron (OSU)
   c. Approval of Agenda and Minutes B. Origer (Chair)
   d. Department Update T. Douglass (OHA)

II. DUR OLD BUSINESS
   a. Benzodiazepine Drug Use Evaluation Follow-Up K. Ketchum (OSU)
      1. Drug Use Evaluation
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA
   b. Lovaza PA Criteria M. Herink (OSU)
      1. PA criteria
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA

III. DUR NEW BUSINESS
   a. Diclofenac Safety Evaluation K. Sentena (OSU)
      1. Safety Evaluation
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA
   b. Antipsychotic Adherence Monitoring RetroDUR Proposal T. Williams (OSU)
      1. Proposal
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA
   c. Zolpidem Drug Use Evaluation K. Ketchum (OSU)
      1. Drug Use Evaluation
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA
d. Immunoglobulin Abbreviated Class Review B. Fouts (OSU)
   1. Class Review
   2. Public Comment
   3. Discussion of Clinical Recommendations to OHA

e. Immunoglobulin Drug Use Evaluation K. Ketchum (OSU)
   1. Drug Use Evaluation
   2. Public Comment
   3. Discussion of Clinical Recommendations to OHA

IV. PREFERRED DRUG LIST OLD BUSINESS M. Herink (OSU)
   a. Hepatitis C Class Update
      1. New Guidelines
      2. Class Update
      3. Public Comment
      4. Discussion of Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS M. Herink (OSU)
   a. Vitamins Abbreviated Class Review
      1. Class Review
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA

   b. Inhaled Antibiotics M. Herink (OSU)
      1. Class Update
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA

   c. Procysbi (delayed-release cysteamine bitartrate) S. Willard (OSU)
      1. New Drug Evaluation
      2. Public Comment
      3. Discussion of Clinical Recommendations to OHA

   d. Topical Antifungals Class Update B. Liang (OSU)
      1. Luliconazole (Luzu) New Drug Evaluation
      2. Class Update
      3. Public Comment
      4. Discussion of Clinical Recommendations to OHA

   e. Drug Class Scans M. Herink (OSU)
      1. Smoking Cessation
      2. Quick relief medications for asthma
      3. Long-Acting opioids
      4. Proton Pump Inhibitors
      5. GI – digestive enzymes
      6. Public Comment
      7. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN
MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD; Zahia Esber, MD

Members Present by Phone: David Pass, MD; Joshua Bishop, PharmD; James Slater, PharmD; William Nunley, MD

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Hank Hickman; Amanda Meeker, PharmD;

Staff Present by Phone: Kathy Sentena, PharmD, Bing-Bing Liang, PharmD; Sherri Argyres, PharmD; Shannon Jasper

Audience: Tim McFerron, (Alkermes); Jeana Colabianchi (Sunovion); Lyle Laird (Sunovion)*; Aaron Shaw (Sunovion); Kim Laubmeier (Otsuka)*; Justine Overman (Astra Zeneca); Tom McLean (Gilead)*; Amy Bauman (Gilead); Troy Larsen (Takeda); Barry Benson (Merck); Paul Barham (Novo Nordisk); Kyle Linhardt (Upsher Smith); D.R. McCale (Baxter); Venus Holder (Eli Lilly); Amy Everitt (Otsuka); Leslie Mann (Celgene); Mike Willett (Pfizer); Amy Burns (AllCare); Kim Blood (WVCH); Caryn Mickelson (WOAH); Loren Sandt (Caring Ambassadors)*; Annie Ogostalick; Bruce Smith (GlaxoKlineSmith); Steve Faloon (OAPI); Kurt Turner (OAPI); Ha Trinh (Salud Pharmacy intern); Dean Haxby (OSU / OHSU); Troy Pendegraft (Nipro Diagnostics); Ann Marie Licos (MedImmune)

(*) Provided verbal testimony

I. CALL TO ORDER
   a. The meeting was called to order at approximately 1:00 pm. Introductions of Committee members and staff.
   b. Mr. Citron reported there are no new conflicts of interest to declare.
   c. Election of Chair and Vice Chair for P&T Committee (page 3)
      Bill Origer, MD reelected Chair, Tracy Klein reelected Vice Chair
II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 10-14)
   Mr. Citron presented the current reports for the utilization summary reports for July 2012 – June 2013. The changes to the report now include the encounter data, rebate data, and physician administered drugs.

b. ProDUR Report (page 15 - 18)
   Mr. Holsapple provided a high level summary for 4th quarter 2013. Reports generated provide early refill, therapy changes, and or loss of medication.

c. RetroDUR Report (page 19)
   Dr. Williams presented the report for 1st quarter Intervention History.

d. Oregon State Drug Reviews (pages 20 – 21)
   1. Update on the New Oral Anticoagulants with a focus on Apixaban®.
      Dr. Sentena presented the newsletter.

III. PREFERRED DRUG LIST

a. Fish Oil (pages 22 – 52)
   Dr. Liang presented the class review regarding the Omega-3 Fatty Acids under the PDL class “Other Lipid Lowering Agents”.

   Recommendations:
   - Keep omega-3 fatty acids as non-preferred agent on PDL, applying the “Non-preferred drugs in PDL classes” prior authorization criteria.
   - Consider listing all over-the-counter fish oil products as non-preferred.

ACTION: Motion, 2nd, All in Favor. Approved.

IV. DUR NEW BUSINESS

a. Fish Oil Drug Use Evaluation (DUE) (pages 53 – 61)
Ms. Ketchum presented the drug use review report for Omega-3 fatty acids. The following recommendations were given:
- Retain legend omega-3 acid ethyl esters (Lovaza®) as non-preferred.
- Put all over-the-counter FO/O3 products on the “Excluded Drug List”. Drugs on this list used for funded diagnoses will be approved through the administrative appeals process.
- Publish an Oregon State Drug Review on FO/O3 detailing the lack of evidence and announcing the policy prior to implementation.
- Bring back Lovaza® as old business to evaluate PA, as we may see a shift in use.

**ACTION:** Motion, 2nd, All in Favor. Approved.

V. PREFERRED DRUG LIST CONTINUED

b. Hepatitis C Abbreviated New Drug Evaluations (pages 77 – 89)
   1. Olysio® (simeprevir) NDE
      Dr. Herink presented the review for simeprevir.
      The following recommendations were given:
      - Apply HepC Protease Inhibitor / Triple Therapy prior authorization criteria and limit use to:
        1. Patients with HCV genotype 1
        2. Without Q80K polymorphism virus
        3. Patients also on peginterferon alfa and ribavirin
        4. Compensated liver disease
        5. Prescribed by a specialist
      - Bring back entire class for further PDL decision making.
      - After executive session:
        Make preferred on PDL and bring back to March P&T meeting as old business. Review report of Hepatitis workgroup. Have staff look into the potential of using a sole source provider.

*ACTION:* After Executive Session, all in favor.

2. Sovaldi® (sofosbuvir) NDE (pages 90 – 104)
   Dr. Herink presented the review for sofosbuvir.
   The following recommendations were given:
   - Make preferred on the PDL and implement prior authorization criteria and limit to:
     1. Patients also on peginterferon and ribavirin with HCV genotype 1 or 4
     2. Patients also on ribavirin with HCV genotypes 2 and 3
     3. Prescribed in consultation with a specialist
     4. Has evidence of moderate to severe fibrosis
   - After executive session:
     The committee decided to bring back to March P&T meeting as old business. Review report of Hepatitis workgroup. Have staff look into the potential of using a sole source provider.

**Public comment:**
Loren Sandt provided public comment on HepC. The presented guidelines are great and please go by the ASLD and ISD recommendations when discussing prices.
Tom McLean from Gilead provided public comment about his company’s product for HepC.

*ACTION: After Executive Session, all in favor.

   Dr. Argyres presented the review for bedaquiline.
   The following recommendations were given:
   1. Prior authorize bedaquiline to limit its use to patients infected with active pulmonary MDR M. tuberculosis when
      a) an affective antimycobacterial regimen cannot otherwise be provided and
      b) the drug is used in association with an MDR-TB regimen that includes at least 3 drugs to which the patient’s MDR-TB isolate is susceptible to in vitro or, if in vitro testing is unavailable, 4 other drugs to which the patient’s isolate is likely susceptible.
   2. Documentation of the following should be approved:
      a) Diagnosis of active pulmonary MDR-TB (i.e., not latent or drug sensitive TB)
      b) Resistance of the patient’s isolate to at least isoniazid and rifampin
      c) Susceptibility of the patient’s isolate to bedaquiline
      d) Prescriptions for 3 or 4 concomitant medications used to treat MDR-TB
      e) The use of expert medical consultation
   3. Make bedaquiline non-preferred and consider reviewing the entire class in the future to identify preferred options.
   4. Approve as printed.

   ACTION: Motion, 2nd, All in Favor. Approved.

c. Second Generation Antipsychotics (pages 105 – 126)
   Dr. Meeker presented the class update for Second Generation Antipsychotics.
   The following recommendations were given:
   1. Based on the lack of long-term effectiveness and safety data, recommend listing aripiprazole long-acting injection as non-preferred on the voluntary PDL.
   2. Evaluate costs in executive session.
   After executive session:
   Make ziprasidone Non-Preferred on the Voluntary MH PDL.

   Public comment:
   Dr. Lyle Laird from Sunovion spoke in regards to the Second Generation Antipsychotics and the statistics regarding Bipolar disorder, Bipolar depression, measures of anxiety, quality of life and measure of suicide.
   Dr. Kim Laubmeier from Otsuka spoke regarding Abilify®, the boxed warnings and asked if there were questions.

   *ACTION: After Executive Session, all in favor.

d. Gout Medications (pages 127 – 133)
   Dr. Herink presented the review for Analgesics for Gout.
   The following recommendations were given:
   1. Therapy with xanthine oxidase inhibitors remains first-line therapy for chronic gout / hyperuricemia
   2. There is sufficient evidence of any significant difference between allopurinol and feboxostat in clinical outcomes such as gout flares.
Rheumetology guidelines give no preference to either agent and both are recommended as first line treatment.

3. There is insufficient evidence for the treatment of intra-articular corticosteroids for the treatment of acute gout.

4. No further review or research needed. Evaluate comparative costs in executive session.

After executive session, no changes to PMPDP were recommended.

*ACTION: After Executive Session, all in favor.

e. Drug Class Scans
   1. Oral Antivirals HSV
      Dr. Herink presented the review.
      The following recommendations were given:
      - No further research or review needed at this time.
      - Evaluate comparative costs in executive session.

      After executive session, there were no changes recommended to the PMPDP.

*ACTION: After Executive Session, all in favor.

2. Hormone Replacement Therapy
   Dr. Herink presented the review.
   The following recommendations were given:
   - There is no new significant comparative evidence on the efficacy and safety of hormone replacement therapy medications; no further research or review needed at this time.
   - Evaluate comparative costs in executive session.

   After executive session:
   - Make FemHRT, Jintelli and their generics non preferred on PMPDP and grandfather for 12 months.
   - Make Vivelle-Dot and Alora preferred on PMPDP.

*ACTION: After Executive Session, all in favor.

3. Calcium Channel Blockers
   Dr. Herink presented the review.
   The following recommendations were given:
   - No further research or review needed at this time.
   - Evaluate comparative costs in executive session.

   After executive session, there are no changes to PMPDP.

*ACTION: After Executive Session, all in favor.

4. Beta-Blockers
   Dr. Herink presented the review.
   The following recommendations were given:
   - No further research or review is needed at this time.
   - Evaluate comparative costs in executive session.

   After executive session:
   - Make nadolol nonpreferred on PMPDP and grandfather for 12 months.
*ACTION: After Executive Session, all in favor.

5. ACEI / ARBs / DRIs  
Dr. Herink presented the review.  
The following recommendations were given:  
- No further research or review needed at this time.  
- There is insufficient evidence evaluating azilsartan / chlorthalidone combination therapy on long term clinical outcomes. Maintain as non-preferred and evaluate comparative costs in executive session.  
- There is no new comparative efficacy or safety evidence for preference of one agent over another within each class.  

After executive session:  
- Make captopril, fosinopril, moexilpril, quinapril, trandolapril and their HCTZ combination products non-preferred due to low use and high relative price and grandfather for 12 months.

*ACTION: After Executive Session, all in favor.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

Mr. Citron confirmed the next P & T meeting will be held on March 27, 2014.

VII. ADJOURN
OHP Benzodiazepine Drug Use Evaluation: Follow-up

This is a follow-up to a benzodiazepine (BZO) drug use evaluation presented to the Committee in November 2013 that found 37.5% of patients on a BZO used it longer than 90 days despite little evidence to support use longer than 8 weeks. The mean length of long-term use was 256 days (8.5 months). The most commonly used long-term BZOs were all highly potent, short acting drugs.

In an effort to prevent inappropriate long-term BZO use, it was recommended to implement a prior authorization for prescriptions extending beyond 4 weeks for newly started patients (no history within last 100 days). Approval would be granted in any of the three situations:

1. Diagnosis of malignant neoplasm or other end of life diagnosis
2. Diagnosis of epilepsy
3. OHP Covered Indication and all of the following
   - Rationale to support long-term BZO use for the supplied indication(s)
   - No concurrent sedative/hypnotic or opioid
   - Dose < 3mg diazepam equivalents

The Committee asked for more data to determine if there were any discernible patterns of long-term BZO prescribing in geography or provided specialty.

Results:

Table 1 reports the top 10 specialties of the prescriber on BZO claims by claim count. Only BZO claims for patients identified with long-term therapy in the previous DUE were included. Patients may access more than one prescriber so the “patient” cannot be used for the unit of analysis. However, only one prescriber is listed on the claim. The top 10 prescriber specialties accounts for 88% of all claims. There is a high “UNKNOWN” specialty because of the high number of managed care claims included. Primary care physicians account for the highest number of claims with Family Practice (22%) and Internist (12%). Nurse Practitioners (11%), Family Nurse Practitioners (8%) and Advance Practice Nurses (6%) are the next highest group. Mental Health providers were third with Psychiatrists (10%) and Psychiatric Mental Health Nurse Practitioners (6%). The percentage drops to less than 1% of claims per specialty after the top 10. Emergency Medicine ranked 12th with 638 claims (0.7%).
# Table 1: Study Group Patients - By Prescriber Specialty

<table>
<thead>
<tr>
<th>Rank</th>
<th>Prescriber Specialty</th>
<th>Unique Patients</th>
<th>%</th>
<th>Claim count</th>
<th>%</th>
<th>Total Amount Paid</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n= 7,559</td>
<td></td>
<td>89,644</td>
<td></td>
<td>$1,036,214</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Family Practitioner</td>
<td>2,452</td>
<td>32.4%</td>
<td>19,640</td>
<td>21.9%</td>
<td>$240,729</td>
<td>23.2%</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>1,396</td>
<td>18.5%</td>
<td>9,341</td>
<td>10.4%</td>
<td>$77,642</td>
<td>7.5%</td>
</tr>
<tr>
<td>3</td>
<td>Internist</td>
<td>1,283</td>
<td>17.0%</td>
<td>10,307</td>
<td>11.5%</td>
<td>$120,977</td>
<td>11.7%</td>
</tr>
<tr>
<td>4</td>
<td>Nurse Practitioner</td>
<td>1,296</td>
<td>17.1%</td>
<td>9,704</td>
<td>10.8%</td>
<td>$108,753</td>
<td>10.5%</td>
</tr>
<tr>
<td>5</td>
<td>Psychiatrist</td>
<td>1,015</td>
<td>13.4%</td>
<td>8,976</td>
<td>10.0%</td>
<td>$109,346</td>
<td>10.6%</td>
</tr>
<tr>
<td>6</td>
<td>Family Nurse Practitioner</td>
<td>1,119</td>
<td>14.8%</td>
<td>7,004</td>
<td>7.8%</td>
<td>$79,827</td>
<td>7.7%</td>
</tr>
<tr>
<td>7</td>
<td>Psychiatric Mental Health Nurse Practitioner</td>
<td>634</td>
<td>8.4%</td>
<td>5,331</td>
<td>5.9%</td>
<td>$74,745</td>
<td>7.2%</td>
</tr>
<tr>
<td>8</td>
<td>Advance Practice Nurse</td>
<td>655</td>
<td>8.7%</td>
<td>4,929</td>
<td>5.5%</td>
<td>$54,098</td>
<td>5.2%</td>
</tr>
<tr>
<td>9</td>
<td>Physician Assistants</td>
<td>724</td>
<td>9.6%</td>
<td>3,781</td>
<td>4.2%</td>
<td>$43,921</td>
<td>4.2%</td>
</tr>
<tr>
<td>10</td>
<td>Physician</td>
<td>496</td>
<td>6.6%</td>
<td>3,326</td>
<td>3.7%</td>
<td>$39,932</td>
<td>3.9%</td>
</tr>
</tbody>
</table>
Table 2 reports the top 10 counties by claim count per rounded enrollment for Nov 2013. It suggests that Benton, Lake and Lincoln counties may have higher prevalence of chronic BZO use. But, these counties represent small absolute numbers of chronic use patients.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Prescriber County</th>
<th>Claim Count</th>
<th>Claim Count / Enrollment</th>
<th>Estimated Enrollment Nov 2013</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benton</td>
<td>3,500</td>
<td>0.50</td>
<td>7000</td>
<td>3.9%</td>
</tr>
<tr>
<td>2</td>
<td>Lake</td>
<td>382</td>
<td>0.38</td>
<td>1000</td>
<td>0.4%</td>
</tr>
<tr>
<td>3</td>
<td>Lincoln</td>
<td>1,942</td>
<td>0.22</td>
<td>9000</td>
<td>2.2%</td>
</tr>
<tr>
<td>4</td>
<td>Josephine</td>
<td>3,687</td>
<td>0.19</td>
<td>19000</td>
<td>4.1%</td>
</tr>
<tr>
<td>5</td>
<td>Harney</td>
<td>191</td>
<td>0.19</td>
<td>1000</td>
<td>0.2%</td>
</tr>
<tr>
<td>6</td>
<td>Tillamook</td>
<td>745</td>
<td>0.19</td>
<td>4000</td>
<td>0.8%</td>
</tr>
<tr>
<td>7</td>
<td>Coos</td>
<td>2,178</td>
<td>0.17</td>
<td>13000</td>
<td>2.4%</td>
</tr>
<tr>
<td>8</td>
<td>Lane</td>
<td>9,368</td>
<td>0.16</td>
<td>58000</td>
<td>10.5%</td>
</tr>
<tr>
<td>9</td>
<td>Wheeler</td>
<td>29</td>
<td>0.15</td>
<td>200</td>
<td>0.0%</td>
</tr>
<tr>
<td>10</td>
<td>Jackson</td>
<td>5,643</td>
<td>0.14</td>
<td>39000</td>
<td>6.3%</td>
</tr>
<tr>
<td>10</td>
<td>Curry</td>
<td>421</td>
<td>0.14</td>
<td>3000</td>
<td>0.5%</td>
</tr>
<tr>
<td>10</td>
<td>Douglas</td>
<td>2,787</td>
<td>0.14</td>
<td>20000</td>
<td>3.1%</td>
</tr>
</tbody>
</table>
Table 3 displays the top 10 NPIs by claim count. It demonstrates that chronic use prescribing is widely distributed. In fact, the top 50 NPIs account for less than 18% of all claims.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Specialty</th>
<th>County</th>
<th>Unique Patients</th>
<th>% Claim Count</th>
<th>% Total Amount Paid</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=</td>
<td>7,559</td>
<td>89,644</td>
</tr>
<tr>
<td>1</td>
<td>Nurse Practitioner (default Spec)</td>
<td>Lane</td>
<td>67</td>
<td>0.9%</td>
<td>712</td>
<td>0.8%</td>
</tr>
<tr>
<td>2</td>
<td>Psychiatrist</td>
<td>Benton</td>
<td>62</td>
<td>0.8%</td>
<td>676</td>
<td>0.8%</td>
</tr>
<tr>
<td>3</td>
<td>Family Practitioner</td>
<td>Marion</td>
<td>96</td>
<td>1.3%</td>
<td>586</td>
<td>0.7%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Multnomah</td>
<td>58</td>
<td>0.8%</td>
<td>547</td>
<td>0.6%</td>
</tr>
<tr>
<td>5</td>
<td>Psychiatric Mental Health Nurse Practitioner</td>
<td>Lane</td>
<td>42</td>
<td>0.6%</td>
<td>497</td>
<td>0.6%</td>
</tr>
<tr>
<td>6</td>
<td>Internist</td>
<td>Washington</td>
<td>41</td>
<td>0.5%</td>
<td>491</td>
<td>0.5%</td>
</tr>
<tr>
<td>7</td>
<td>Nurse Practitioner (default Spec)</td>
<td>Washington</td>
<td>44</td>
<td>0.6%</td>
<td>474</td>
<td>0.5%</td>
</tr>
<tr>
<td>8</td>
<td>Family Nurse Practitioner</td>
<td>Lane</td>
<td>50</td>
<td>0.7%</td>
<td>473</td>
<td>0.5%</td>
</tr>
<tr>
<td>9</td>
<td>Psychiatric Mental Health Nurse Practitioner</td>
<td>Marion</td>
<td>39</td>
<td>0.5%</td>
<td>428</td>
<td>0.5%</td>
</tr>
<tr>
<td>10</td>
<td>Advance Practice Nurse</td>
<td>Washington</td>
<td>60</td>
<td>0.8%</td>
<td>428</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Discussion:
Primary care physicians and nurse practitioners are the primary prescribers of long-term BZOs. However, this prescribing appears to be widely distributed and not concentrated by individual or geography.

In addition, internal reviewers identified three areas of concern in the previous recommendations. First the 3mg diazepam equivalent dose limit is appropriate for patients over 65 years old only. It was recommended to edit or delete this requirement from the approval criteria. Secondly, to avoid false positive identification of “new patients” from mail order claims, it was recommended to extend the look back period to 120 days from 100 days. Finally, it was recommended that automated provider education letters be sent to the prescriber when a patient is identified as a new patient and will be limited to 4 weeks of therapy without a prior authorization request in order to avoid unnecessary gaps in therapy for appropriate patients.
Omega-3 Fatty Acids

**Goal(s):**
- Promote safe and effective therapies for lipid lowering agent.

**Length of Authorization:** 1 year

**Requires PA:**
- Omega-3-Acid Ethyl Esters (Lovaza®)
- Icosapent Ethyl (Vascepa®)

**Covered Alternatives:** Listed at: [http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml](http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml)

**Approval Criteria**

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the diagnosis?</td>
<td>Record ICD-9 code</td>
</tr>
<tr>
<td>2. Is the diagnosis an OHP covered diagnosis?</td>
<td>Yes: Go to #3. No: Pass to RPh, Deny for OHP Coverage.</td>
</tr>
<tr>
<td>3. Will the prescriber consider a change to a preferred product? Message:</td>
<td>Yes: Inform provider of covered alternatives in class <a href="http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html">http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html</a> No: Go to #4</td>
</tr>
<tr>
<td>4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dl?</td>
<td>Yes: Go to #5 No: Pass to RPh; Deny for Medical Appropriateness</td>
</tr>
<tr>
<td>5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at maximum tolerable dose (as seen in dosing table below). AND niacin 1-2 mg/day OR Is patient taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy.</td>
<td>Yes: Approve up to 1 year. No: Deny for Medical Appropriateness. Recommend untried agent(s).</td>
</tr>
</tbody>
</table>

### Table 1: Dosing of fenofibrate and derivatives for hypertriglyceridemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antara (micronized)</td>
<td>43-130 mg once daily</td>
<td>130 mg once daily</td>
</tr>
<tr>
<td>Fenoglide</td>
<td>40-120 mg once daily</td>
<td>120 mg once daily</td>
</tr>
<tr>
<td>Fibricor</td>
<td>25-105 mg once daily</td>
<td>105 mg once daily</td>
</tr>
<tr>
<td>Lipofen</td>
<td>50-150 mg once daily</td>
<td>150 mg once daily</td>
</tr>
<tr>
<td>Lofibra (micronized)</td>
<td>67-200 mg once daily</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Lofibra (tablets_)</td>
<td>54-160 mg once daily</td>
<td>160 mg once daily</td>
</tr>
<tr>
<td>TriCor</td>
<td>48-145 mg once daily</td>
<td>145 mg once daily</td>
</tr>
<tr>
<td>Triglide</td>
<td>50-160 mg once daily</td>
<td>160 mg once daily</td>
</tr>
<tr>
<td>Trilipix</td>
<td>45-135 mg once daily</td>
<td>135 mg once daily</td>
</tr>
</tbody>
</table>

**P&T Action:** 3-27-2014

**Revision(s):**

**Initiated:**

Diclofenac Safety Evaluation

Month/Year of Review: May 2014
Last Class Review: Nonsteroidal Antiinflammatory Drugs November 2013
End date of literature search: February 2014
Source: DURM Drug Class Scan

Current Preferred Drug List (PDL) Status:

<table>
<thead>
<tr>
<th>Diclofenac Formulations</th>
<th>PDL Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Potassium</td>
<td>Preferred</td>
</tr>
<tr>
<td>Diclofenac Sodium DR</td>
<td>Preferred</td>
</tr>
<tr>
<td>Diclofenac Topical (patch)</td>
<td>Non-preferred</td>
</tr>
<tr>
<td>Diclofenac Topical (gel)</td>
<td>Non-preferred</td>
</tr>
<tr>
<td>Diclofenac/misoprostol</td>
<td>Non-preferred</td>
</tr>
<tr>
<td>Diclofenac ER 24H</td>
<td>Non-preferred</td>
</tr>
</tbody>
</table>

Research Questions:
- What are safety concerns specific to diclofenac that need to be considered?
- Should diclofenac require a prior authorization due to safety risks?
- Should the PDL change in response to diclofenac safety concerns?

Conclusions:
- A meta-analysis of randomized controlled trials showed diclofenac to be associated with an increased incidence of major vascular events (driven by coronary events) and death due to vascular causes, similar to those seen with selective COX-2 inhibitors, such as celecoxib. Naproxen was shown to confer less cardiovascular (CV) risk.¹
- A meta-analyses of observational data showed diclofenac to have a higher risk of acute myocardial infarction (MI) than other commonly used NSAIDS.²
- Gastrointestinal (GI) risks were similar for diclofenac compared to other NSAIDS.³
Recommendations:
- Due to limited evidence on safety data associated with diclofenac therapy and the inherent risks associated with all NSAIDS, no changes to the preferred drug list are recommended at this time.

Reason for Review:
Nonsteroidal anti-inflammatory drugs (NSAIDS) were reviewed as part of a drug class scan (November 2013) and recent DERP report. Pharmacy and Therapeutics (P&T) members were concerned over safety issues surrounding diclofenac treatments. This review will clarify the safety risk of diclofenac. Available evidence will be analyzed and used to recommend the potential need for prior authorization criteria and/or changes to the PDL.

Previous 2013 Drug Class Scan Conclusions:
- Non-selective NSAIDS were associated with a similar increased risk of serious GI events and all but naproxen were associated with similar increased risk of serious cardiovascular (CV) events.
- Celecoxib does not appear to be associated with a higher risk of CV events and is gastroprotective in the short term compared with non-selective NSAIDS.
- Nabumetone was shown to be gastroprotective compared to non-selective NSAIDS.

Background:
NSAIDS are common pain relievers used for many ailments. NSAID use has been associated with a variety of adverse effects thought to be due to the inhibition of the COX-1 and COX-2 enzyme. Common selective and non-selective NSAIDS such as diclofenac, ibuprofen, naproxen and celecoxib all carry a black box warning of the potential to cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke which may result in death. This risk may be increased in those with CV disease, or risk factors for CV disease, and in those with a longer history of NSAID use. NSAIDS also carry a warning against the risk of severe GI events including bleeding, ulceration, and perforation of the stomach or intestines which can be fatal.

Studies have suggested that selective NSAIDS (COX-2 inhibitors) carry an increased risk of vascular events versus traditional non-selective NSAIDS (inhibit COX-1 and COX-2). However, a 2005 FDA review of long-term clinical trials found that selective NSAIDS aren’t definitively associated with increased CV risk and suggested that this may be a NSAID class effect. These findings were echoed in a 2011 AHRQ review in patients with osteoarthritis which found for the outcomes of myocardial infarction (MI), other CV events, or cerebrovascular events, celecoxib was similar to nonselective NSAIDS. Evidence A meta-analysis of cardiovascular safety and NSAIDS found no statistically significant difference in CV adverse events amongst the different NSAIDS studied. A 2010 Drug Effectiveness Review Project (DERP) report found moderate strength of evidence to suggest that all non-selective NSAIDS, excluding naproxen, are associated with increased CV risk, similar to selective NSAIDS. A 2011 systematic review of observational studies found diclofenac to have the fourth highest association of diclofenac with cardiovascular risk has been suggested for almost ten years. In patients with a history of cardiovascular disorders, diclofenac has been shown to increase the risk of subsequent events. A retrospective claims analysis among Danish patients showed diclofenac use in patients with prior MI to be associated with the highest risk of death or recurrent MI, compared to other NSAIDS. Diclofenac use in patients without a history of CV disease has also been implicated in conferring increased CV risk. An increase in vascular events with diclofenac over placebo (RR 1.63, 95% CI 1.12 to 2.72) was shown in an indirect analysis of patients without a history of CV disease. A 2011 systematic review of observational studies found diclofenac to have the fourth highest

Author: Kathy Sentena
March 2014
relative risk of CV events (RR 1.40, 95% CI 1.27 to 1.55), with etoricoxib, etodolac and rofecoxib conferring a higher risk. The CV risk with diclofenac appears to be dose-dependent with an increased risk demonstrated at doses of 100mg daily and higher.

Methods:
A Medline literature search ending in February 2014 for new systematic reviews and randomized controlled trials (RCTs) related to diclofenac safety was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for safety alerts and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: three systematic reviews, one guideline, and two safety alerts.

Systematic Reviews:

Vascular and Upper Gastrointestinal Effects of Non-steroidal Anti-inflammatory Drugs: Meta-Analyses of Individual Participant Data from Randomised Trials
A 2013 meta-analyses by the Coxib and Traditional NSAID Trialists’ (CNT) Collaboration was done to determine the CV and GI risk of NSAID regimens. Meta-analyses were comprised of 280 randomized trials comparing NSAIDS to placebo and 474 randomized trials of NSAIDS compared to other NSAIDS. Main traditional high-dose NSAIDS evaluated were the following: ibuprofen (2400mg daily), diclofenac (150mg daily) and naproxen (1000mg daily). Included COX-2 inhibitors (coxibs) were: celecoxib (400mg daily), rofecoxib (25mg daily), lumiracoxib (200mg daily), etoricoxib (90mg daily), and valdecoxib (20mg daily). The safety outcomes studied were major CV events (non-fatal MI, non-fatal stroke or vascular death); major coronary events (non-fatal MI or coronary death); stroke; mortality; heart failure; and GI complications (perforation, obstruction, or bleed). The mean patient age was 61 years and primarily comprised of white females. In placebo controlled comparisons, major vascular events were increased with coxibs (RR 1.37, 95% CI 1.14 to 1.66, p=0.0009) and diclofenac (RR 1.41, 95% CI 1.12 to 1.78, p=0.0036). Increased risk was primarily due to increased major coronary events in both coxib and diclofenac groups, RR 1.76 and 1.70, respectively. Ibuprofen was also shown to have increased risk primarily due to major coronary events (RR 2.22, 95% CI 1.10 to 4.48, p=0.0254) and less due to major vascular events (RR 1.44, 95% CI 0.89 to 2.33, p=0.14). There was less patient-years exposure for ibuprofen available for analysis compared to other agents. Risks of major vascular events were not increased with high dose naproxen. Hospitalization risk due to heart failure was increased with coxibs, diclofenac and ibuprofen. Death due to vascular causes was increased by coxibs (RR 1.58, 95% CI 1.00 to 2.49, p=0.0103) and diclofenac (RR 1.65, 95% CI 0.95 to 2.85, p=0.0187). Ibuprofen was associated with an increased risk that was not statistically significant. All-cause mortality was significantly increased for coxibs (RR 1.22) but not for diclofenac or ibuprofen. Naproxen was not associated with an increased risk of death from vascular or any cause of death. Placebo comparisons of GI risk was increased with coxibs and NSAIDS but the highest risk was with ibuprofen and naproxen.

Myocardial Infarction and Individual Nonsteroidal Anti-inflammatory Drugs Meta-Analysis of Observational Studies
A 2013 systematic review and meta-analysis was performed by the Safety of NSAIDS (SOS) project to determine the effect of NSAIDS on acute MI risk. Twenty-five observational cohort or case-control studies were included. Studies were evaluated for quality and methodological limitations. Patients with low-medium to high CV risk were included. Nineteen of the twenty-five studies were rated good for selection and definition of subjects. Of commonly used NSAIDS, the risk of acute MI was the following: etoricoxib (RR 1.97, 95% CI 1.35 to 2.89), etodolac (RR 1.55, 95% CI 1.16 to 2.06), indomethacin (RR 1.40, 95% CI 1.21 to 1.62), diclofenac (RR 1.38, 95% CI 1.26 to 1.52), rofecoxib (RR 1.34, 95% CI 1.22 to 1.48), meloxicam (RR 1.25, 95% CI 1.04 to 1.49), ibuprofen (RR 1.14, 95% CI 0.98 to
1.31), celecoxib (RR 1.12, 95% CI 1.00 to 1.24) and naproxen (RR 1.06, 95% CI 0.94 to 1.20). Diclofenac was also show to have the highest risk of acute MI among new users and second-highest risk, behind rofecoxib, for high-risk populations. Acute MI risk was more common with higher doses of NSAIDS except for diclofenac and rofecoxib, which were associated with an increased risk with low and high doses. Rofecoxib was the only NSAID that showed a dose-response correlation with risk of acute MI. Authors noted the inherent limitations to data provided by observational studies (confounding, selection and information bias).


The Canadian Agency for Drugs and Technology in Healthy (CADTH) reviewed the comparative safety of NSAIDS in a 2013 report and clinical appraisal. Six citations, five systematic reviews and one health technology assessment, met inclusion criteria for the review. Publications included in the review were subject to quality appraisal based on the Assessment of Multiple Systematic Reviews (AMSTAR) tool. NSAIDS included in the review were the following; celecoxib, diclofenac, naproxen, ibuprofen, meloxicam and etodolac. Upper GI and CV harms were the main safety outcomes. Patients with osteoarthritis or rheumatoid arthritis were the most common indication for NSAID use. Celecoxib and high dose diclofenac (150mg daily) were found to be similar in risk for major vascular events; heart failure; all cause mortality and upper GI complications in one meta-analysis. A second meta-analysis found no statistically significant differences between NSAID groups studied and diclofenac in CV adverse events. However, diclofenac was associated with a significantly higher risk of stroke compared to celecoxib. Diclofenac was found to have a higher incidence compared to celecoxib of adverse CV events (pooled ratio of RR 1.15, 95% CI 1.02 to 1.30) in one systematic review of observational studies. This systematic review found that in comparison to ibuprofen and naproxen, diclofenac had a higher overall CV risk. Celecoxib was also compared to other NSAIDS and was found to have similar risk of major vascular events; heart failure and all-cause mortality compared to ibuprofen with less risk of GI complications. Major vascular events were found to be higher in celecoxib compared to naproxen but with a lower incidence of upper GI events. Naproxen had significantly lower risk of CV events compared to diclofenac, ibuprofen, and indomethacin. Most studies included in the systematic reviews were less than 3 months in duration, preventing extrapolation of findings to chronic users of NSAIDS. The authors concluded that the risk of major vascular events with celecoxib were similar to that of diclofenac and ibuprofen but slightly higher than naproxen. The CV risk between non-selective NSAIDS was found to be similar, with the exception of naproxen which was found to have a lower risk.

**New Guidelines:**

**OARSI Guidelines for the Non-surgical Management of Knee Osteoarthritis**

This 2014 guideline updates the previous guideline of 2010. Evidence was graded according to level/type of evidence, quality of evidence (based on Assessment of Multiple Systematic Reviews Tool [AMSTAR] for systematic reviews and Cochrane Risk of Bias Assessment Method for RCTs) and estimated effect sizes (for meta-analyses). Recommendations were based on the RAND/UCLA Appropriateness Method and Delphi voting process. Treatments were assigned one of the following recommendations: appropriate, uncertain or not appropriate. Oral and topical pharmacological treatments deemed appropriate for knee osteoarthritis management were acetaminophen, duloxetine, glucosamine, oral NSAIDS and topical NSAIDS. Good quality evidence found acetaminophen to be an appropriate option, with a low-level of effect, with a lower potential for adverse effects then previously thought. Conservative dosing and limited treatment durations were recommended for use in patients without relevant co-morbidities. Duloxetine was considered an appropriate option for patients without co-morbidities and in patients with multiple-joint osteoarthritis and relevant co-morbidities (fair quality of evidence). Glucosamine was given an uncertain recommendation for symptom relief and not recommended for disease modification based on good evidence. Oral non-selective NSAIDS, were deemed appropriate for patients without co-morbidities, uncertain for those with moderate co-morbidities and not appropriate for patients with high risk of co-morbidities (good quality of evidence). Recommendations were based on evidence of potential for NSAIDS to cause GI, CV and renal adverse effects. Naproxen

Author: Kathy Sentena

March 2014
was found to have less cardiovascular risk than other NSAIDS and diclofenac was associated with the highest incidence of hepatic abnormalities. For selective NSAIDS, appropriate use was recommended in patients without co-morbidities and multiple-joint osteoarthritis with moderate co-morbidity risk, uncertain for those with knee-only osteoarthritis with moderate co-morbidity risk and not recommended for individuals with high co-morbidity risk (good quality of evidence). Evidence found use of selective COX-2 inhibitors to have similar serious adverse event rates as non-selective NSAIDS. Use of NSAIDS, selective and non-selective, according to prescribing limits and utilizing conservative dosing strategies was recommended. Topical NSAIDS were found to be appropriate for knee-only osteoarthritis and uncertain for those with multiple-joint osteoarthritis based on good evidence. Transdermal and oral opioids were given an uncertain recommendation (good quality of evidence).

**Safety Alerts:**

**FDA**
None identified

**European Medicines Agency**
In June 2013 the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) found that diclofenac and COX-2 inhibitors pose similar risks to the cardiovascular system. The risk associated with diclofenac was primarily for high doses (150mg daily), for long-term use and for systemic formulations. They applied the same warning given to COX-2 inhibitors to diclofenac. The PRAC recommended that patients with serious underlying heart or circulatory conditions should not be candidates for diclofenac therapy. Those with high CV risk should use diclofenac cautiously.

**Center of Medicines and Healthcare Products Regulatory Agency (MHRA) Drug Safety Update**
As a result of the above findings, MHRA issued new contraindications and warnings for diclofenac use in individuals with or at risk for CV disease. The agency reported that the after a Europe-wide review they found the CV risk was comparable to that of COX-2 inhibitors. Diclofenac prescribing is contraindicated in patients with: ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or established congestive heart failure (New York Heart Association [NYHA] classification II-IV). The topical gels and creams formulations of diclofenac are excluded from the warning but pertain to all other formulations (tablets, capsules, suppositories and injection).

**New Primary Literature:**
None identified

Author: Kathy Sentena  
March 2014
References:

Author: Kathy Sentena

March 2014
Retrospective Drug Use Review to Improve Antipsychotic Adherence in Patients with Schizophrenia

Policy Goal
- Improve antipsychotic adherence rates for patient with schizophrenia and thereby reduce hospitalizations with a minimal impact on overall healthcare costs

Recommendations
- Create a weekly RetroDUR provider fax notification campaign of potentially non-adherent patients with a recent diagnosis of schizophrenia
- Reporting metrics
  - Provider satisfaction responses
  - HEDIS 2013® Adherence to Antipsychotic Medications for Individuals With Schizophrenia (SAA)
  - Hospitalization rates by antipsychotic adherence level
  - Pre/post hospitalization and prescription utilization rates for patients identified by program for intervention
- Outreach
  - Collaborate with CCO Pharmacy Directors regarding initiative content and timing and inclusion of CCO patients and providers

Background
Schizophrenia represents a significant risk of both severe morbidity and mortality, affecting seven in 1,000 people. Patients with schizophrenia have a higher overall risk of mortality, including an increased risk of suicide. Patients with schizophrenia also have a higher risk of cardiovascular disease. Patients with schizophrenia often have low rates of adherence, short durations of therapy, and high relapse rates. Low adherence is likely due to multiple factors, including symptoms of schizophrenia (e.g. disorganization), intolerance to medications side effects, and a perceived lack of efficacy. The 2009 PORT Schizophrenia guidelines recommend continuous pharmacotherapy indicating lower relapse rates with continuous therapy versus intermittent therapy. PORT guidelines also recommend interventions to improve adherence, though data is insufficient to recommend specific strategies.

The National Committee for Quality Assurance (NCQA) added four antipsychotic-related measures to the 2013 Healthcare Effectiveness Data and Information Set (HEDIS®). Adherence to Antipsychotic Medications for Individuals With Schizophrenia (SAA) was added with the goal of reducing relapse rates, thereby reducing hospitalizations, risks of suicide, and homelessness. NCQA cites a 2004 study of California Medicaid patients which demonstrated significant increases in overall healthcare costs and hospitalization rates in patients with underutilization of antipsychotic medications.

A systematic review of interventions to improve adherence to antipsychotic therapy in patients with schizophrenia found strategies targeting adherence (versus overall care) to be the most effective.
pharmacy-based Veterans Affairs (VA) program used a multiple intervention program to improve adherence. These interventions included unit dose packaging, patient education by a pharmacist, patient refill reminders and provider notifications when prescriptions were not filled on schedule (7-10 days late). Patients were randomized into usual care or intensive management in this study. Blinding was weak, but the study found a difference of 24% in mean medication possession ratio (MPR) between the control and study groups.

For Oregon Medicaid members, antipsychotic medications are paid for by the Fee For Service (FFS) program, regardless of Coordinated Care Organization (CCO) enrollment. Because of this payment structure, CCOs and their providers often have limited and/or delayed access to information on the refill history of the medications. Although the FFS program provides claims history for these medications to the CCOs, the level of integration of this information into the electronic medical record varies by CCO and provider. Provider conversations have indicated that notifications of non-adherence sent to clinicians would be valuable, as the actual refill history is a major gap of information in health care systems that do not have integrated pharmacies.

This drug use evaluation was designed to answer two questions. First, are there patients in the Oregon Medicaid program with a recent diagnosis of schizophrenia who are partially or non-adherent to antipsychotic therapy? Second, are adherence rates associated with increased hospitalizations rates?

Methods

The study enrollment period was 1/1/2011-12/31/2011. Patients with a paid medical claim with a diagnosis of schizophrenia (ICD9 295xx) during the enrollment period were evaluated for inclusion (Figure 1). Of the 9,070 patients with a qualifying diagnosis, 3,250 were included in the study. Administrative exclusions included patients with other health care coverage (Medicare or private insurance) were excluded or with gaps in coverage exceeding 45 days. Patients with a recent diagnosis of dementia, over 64 years old, or under 19 years old were also excluded. Patients with only one antipsychotic claim during the study period were also excluded.

The study period was defined as the 12 months following the patient’s index claim date (IPSD). The IPSD was defined as the first antipsychotic claim during the enrollment period. No distinction was made between newly started therapy and continuation of existing therapy. Antipsychotic claims included point of sale (POS) drug claims and depot antipsychotics bill via the professional claims (PAD AP). PAD AP claims were excluded when the procedure code did not have national drug code (NDC) or the NDC did not match the procedure code.

Adherence was assessed over the study period using proportion of days covered (PDC). The PDC is the number of days a member is covered by at least one antipsychotic medication prescription, divided by the number of days in the study period. The handling of overlapping prescriptions is explained in detail in the data specification in appendix B. PDC differs from medication possession ratio (MPR) in several ways. The most salient being the MPR uses the first and last prescription date, whereas the PDC use the first prescription date and the end date of the study period. MPR may overestimate adherence rates for patients who discontinue...
medications. The PDC has been endorsed by the Pharmacy Quality Alliance as preferred over MPR and was used in the HEDIS 2013 SAA specification.\textsuperscript{7,14} Patients were categorized into 3 levels of adherence:\textsuperscript{13,15}

- Adherent (PDC 80-100%)
- Partially Adherent (PDC 50-79%)
- Non-Adherent (PDC <50%)

Hospitalizations were reported as all cause hospitalizations and schizophrenia hospitalizations. Schizophrenia hospitalizations were identified as hospital encounters within the study period with a primary diagnosis of schizophrenia (ICD9 295). All cause hospitalizations are any hospital encounters during the study period.

![Figure 1. Subject enrollment and exclusion algorithm](image)

**Results**

Patient demographics appear in Table 1. The majority of patients were between 40-59 (55%). Slightly more men were included than women (54%).

Of the 3,250 member included 68% were categorized as adherent (Table 2). Both all cause hospitalizations per member and schizophrenia hospitalizations per member were higher for partially adherent and non-adherent groups compared to the adherent group.
### Baseline Demographics

<table>
<thead>
<tr>
<th>Age at IDSP</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-29</td>
<td>552</td>
<td>17%</td>
</tr>
<tr>
<td>30-39</td>
<td>651</td>
<td>20%</td>
</tr>
<tr>
<td>40-49</td>
<td>882</td>
<td>27%</td>
</tr>
<tr>
<td>50-59</td>
<td>925</td>
<td>28%</td>
</tr>
<tr>
<td>60-64</td>
<td>240</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>#</th>
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<tbody>
<tr>
<td>F</td>
<td>1,507</td>
<td>46%</td>
</tr>
<tr>
<td>M</td>
<td>1,743</td>
<td>54%</td>
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</table>

Table 1 Baseline Demographics

<table>
<thead>
<tr>
<th>PDCAdherence</th>
<th>Members</th>
<th>All Cause Hospitalizations</th>
<th>All Cause Hospitalizations Per Members</th>
<th>Schizophrenia Hospitalizations</th>
<th>Schizophrenia Hospitalizations Per Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-49% - Non-Adherent</td>
<td>441</td>
<td>14%</td>
<td>198</td>
<td>0.45</td>
<td>72</td>
</tr>
<tr>
<td>50-79% - Partially Adherent</td>
<td>586</td>
<td>18%</td>
<td>327</td>
<td>0.56</td>
<td>123</td>
</tr>
<tr>
<td>80-100% - Adherent</td>
<td>2,223</td>
<td>68%</td>
<td>705</td>
<td>0.32</td>
<td>240</td>
</tr>
</tbody>
</table>

Table 2 Adherence Levels and Associated Hospitalizations
The proportion of patients who were adherent to antipsychotic therapy trended downward as the number of hospitalizations during the study period increased (figure 2).

**Discussion**

Nearly 1 in 3 patients included in this study was classified as non-adherent or partially adherent. These patients are more likely to be hospitalized than patients who are adherent. This is true for both schizophrenia and non-schizophrenia related hospitalizations. The hospitalization rates observed in partially and non-adherent patients may be indicative of poorer symptom control and lower quality of life. This represents a significant opportunity to improve care for patients.

There are several limitations to this analysis. As with any retrospective claims analysis, diagnosis information may not accurately reflect the true clinical diagnosis, both including patients without schizophrenia and excluding patient with schizophrenia. A paid pharmacy claim may not correspond to a patient actually taking a medication. The use of medication samples and inpatient hospitalizations may also produce apparent gaps in therapy where none exists. Submission of medical claims is commonly delayed up to 6 months. This is particularly problematic for patient receiving depot antipsychotics which are not billed to the FFS program by
a pharmacy. Despite these limitations, there appears to be sufficient opportunity to notify providers of potential adherence issues.

**Recommendations**

A RetroDUR provider fax campaign represents a cost-effective notification system highlighting potentially non-adherent patients. Each week the provider will receive a fax for any patients with a history of partial or non-adherence who are at least 7 days late refilling an ongoing antipsychotic prescription. Patients with a recent history of antipsychotic adherence exceeding 80% (i.e. adherent patients) will generate a notification only after the prescription is fourteen days late. The provider report (appendix A) contains three sections. The first section identifies the patient and describes the RetroDUR program. The second page shows the patient’s recent antipsychotic refill history, contact information for recent pharmacies and a feedback form. The third page contains educational materials on the Medicaid formulary, medication costs, and strategies to increase adherence.

Faxes will initially be sent only to select pilot sites. The program will be refined through working closely with these pharmacies. The program will be expanded to a larger audience as the program matures. Discussions with several pilot sites are ongoing.

RetroDUR activity reports will include:

- Patient Identified
- Provider messages sent
- Provider response rate
- Number of providers who found the information useful

Improvements to quality will be measured by two reports. Adherence to antipsychotic therapy as measures by the HEDIS SAA specification will be reported on a quarterly basis (Table 3). The detailed specification appears in appendix B.

<table>
<thead>
<tr>
<th>Adherence Level</th>
<th>Quarter 1 Oct - Dec</th>
<th>Quarter 2 Jan - Mar</th>
<th>Quarter 3 Apr - Jun</th>
<th>Quarter 4 Jul - Sep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#  %</td>
<td>#  %</td>
<td>#  %</td>
<td>#  %</td>
</tr>
<tr>
<td>0-49% - Non-Adherent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-79% - Partially Adherent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-100% - Adherent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Sample HEDIS SAA Quarterly Report Format

A pre/post report of antipsychotic adherence for patients who are identified by the program will be generated annually. Data elements will be similar to table 2 in the results section.
References


Appendix A: Antipsychotic Adherence Monitoring Provider Report

Date: mm/dd/yyyy

Attention: Dr. X
Fax: 541-123-4567

Re: Patient John Doe has not filled Drug X since MM/DD/YY (ZZ days late as of mm/dd/yy)

Pharmacy claims data identified Dr. X as the most recent prescriber of Drug X for John Doe. Pharmacy claims as of MM/DD/YYYY indicate Drug X is ZZ days past due. The following page contains the last 12 months of refill history for John Doe as of MM/DD/YYYY including the antipsychotic fill history for your patient, and the medication possession ratio (MPR) of each medication. MPR is a calculation based upon the total days covered by medication in the treatment period divided by total days in the treatment period.

The Oregon Medical Assistance Program (MAP) is providing prescribers information on adherence to antipsychotics for their Medicaid patients to facilitate increased adherence rates. The goal of increasing adherence is to reduce relapse rates, thereby reducing hospitalizations, risks of suicide, and homelessness, and increasing quality of care.

References:
- The National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS®) 2013 “Adherence to Antipsychotic Medications for Individuals With Schizophrenia (SAA)”
Medication Adherence Report as of MM/DD/YYYY

Patient:  John Doe    DOB 1/1/1965    Member ID XYZ1234

Please note: Medications prescribed as needed may falsely appear as not having been filled on schedule. Intentionally discontinued medications may also appear on this report.

Fill History for John Doe DOB 1/1/1965

<table>
<thead>
<tr>
<th>Pharmacy Information</th>
<th>Drug Name</th>
<th>Rx Number</th>
<th>Last Rx Fill Date</th>
<th>Days Supply Filled</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC Pharmacy</td>
<td>Quetiapine Fumarate</td>
<td>789</td>
<td>mm/dd/yyyy</td>
<td>xx</td>
</tr>
<tr>
<td>Portland, OR</td>
<td></td>
<td>ISBN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone: 503-234-5678</td>
<td></td>
<td>ISBN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fax: 503-234-5679</td>
<td></td>
<td>ISBN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XYZ Pharmacy</td>
<td>Lurasidone</td>
<td>456</td>
<td>mm/dd/yyyy</td>
<td>xx</td>
</tr>
<tr>
<td>Portland, OR</td>
<td></td>
<td>ISBN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone: 503-111-2222</td>
<td></td>
<td>ISBN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fax: 503-111-2223</td>
<td>Risperidone</td>
<td>123</td>
<td>mm/dd/yyyy</td>
<td>xx</td>
</tr>
</tbody>
</table>

Please check all that apply:

☐ This information was useful
☐ I was unaware of the patient’s refill history
☐ The educational information (page 3) was valuable
☐ Other __________________________________________

Please fax feedback to the Medical Assistance Program at 503-947-2596.
For questions regarding this report or policy please call 503-945-6513.
Strategies to Increase Adherence

- Minimize Financial Barriers by using the Mental Health Preferred Drug List (PDL)
  - Preferred antipsychotics do not have a co-pay
  - Non-preferred antipsychotics have a patient copay which may reduce adherence
- Select drugs with low discontinuation rates
  - Initial therapy should be patient specific to minimize side effects, as few differences in short-term efficacy among the atypical antipsychotics have been demonstrated in patients with schizophrenia
  - Clozapine and olanzapine consistently result in lower discontinuation rates compared with other antipsychotics in patients failing to respond to initial therapy, especially in long-term studies
- Improve consistency and accountability with Pill Boxes and pill counts
- Use long acting depots in select populations
  - There are no known differences among the efficacy of long acting antipsychotic formulations of fluphenazine, haloperidol, aripiprazole, risperidone, paliperidone, and olanzapine.
  - Should be used in patients who are on a stable dose of oral medication before being switched
- Minimize Adverse Effects
  - Tardive dyskinesia: If patients experience, decrease the dose or switch to another SGA
  - Weight gain: Interventions may include nutritional counseling, initiation of exercise program, medications that promote weight loss, and/or a change of the antipsychotic medication to one that is less associated with weight gain

Antipsychotic costs are listed above along with voluntary PDL status. Non-preferred medications require a patient copayment. Please visit our website, www.orpdl.org, for the complete PDL.

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Drug Name</th>
<th>Pharmacy Average Actual Acquisition Costs for a 1 Month Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Risperidone</td>
<td>$5</td>
</tr>
<tr>
<td>Y</td>
<td>Olanzapine</td>
<td>$9</td>
</tr>
<tr>
<td>Y</td>
<td>Fluphenazine</td>
<td>$13</td>
</tr>
<tr>
<td>Y</td>
<td>Quetiapine Fumarate</td>
<td>$18</td>
</tr>
<tr>
<td>Y</td>
<td>Haloperidone Decanoate</td>
<td>$33</td>
</tr>
<tr>
<td>Y</td>
<td>Haloperidol Decanoate</td>
<td>$33</td>
</tr>
<tr>
<td>Y</td>
<td>Haloperidol</td>
<td>$44</td>
</tr>
<tr>
<td>Y</td>
<td>Clozapine</td>
<td>$49</td>
</tr>
<tr>
<td>Y</td>
<td>Loxapine Succinate</td>
<td>$60</td>
</tr>
<tr>
<td>N</td>
<td>Clozapine ODT</td>
<td>$107</td>
</tr>
<tr>
<td>N</td>
<td>Risperidone ODT</td>
<td>$117</td>
</tr>
<tr>
<td>Y</td>
<td>Perphenazine</td>
<td>$121</td>
</tr>
<tr>
<td>Y</td>
<td>Chlorpromazine</td>
<td>$148</td>
</tr>
<tr>
<td>Y</td>
<td>Ziprasidone</td>
<td>$174</td>
</tr>
<tr>
<td>Y</td>
<td>Loxapine Succinate</td>
<td>$186</td>
</tr>
<tr>
<td>N</td>
<td>Olanzapine ODT</td>
<td>$241</td>
</tr>
<tr>
<td>N</td>
<td>Quetiapine Fumarate (Seroquel XR*)</td>
<td>$387</td>
</tr>
<tr>
<td>N</td>
<td>Risperidone Microspheres (Risperdal Consta*)</td>
<td>$430</td>
</tr>
<tr>
<td>N</td>
<td>Lurasidone (Latuda*)</td>
<td>$610</td>
</tr>
<tr>
<td>N</td>
<td>Paliperidone (Invega*)</td>
<td>$668</td>
</tr>
<tr>
<td>N</td>
<td>Asenapine Maleate(Saphris*)</td>
<td>$674</td>
</tr>
<tr>
<td>N</td>
<td>Iloperidone ( Fanap*)</td>
<td>$695</td>
</tr>
<tr>
<td>N</td>
<td>Aripiprazole (Abilify*)</td>
<td>$740</td>
</tr>
<tr>
<td>N</td>
<td>Aripiprazole (Abilify Discmelt*)</td>
<td>$791</td>
</tr>
<tr>
<td>N</td>
<td>Olanzapine Pamoate (Zyprexa Relprev*)</td>
<td>$970</td>
</tr>
<tr>
<td>N</td>
<td>Paliperidone Palmitate (Invega Sustenna*)</td>
<td>$1,409</td>
</tr>
<tr>
<td>N</td>
<td>Aripiprazole (Abilify Maintena*)</td>
<td>$1,523</td>
</tr>
</tbody>
</table>

ODT = Orally disintegrating tablet

<table>
<thead>
<tr>
<th>Concern and/or Risk</th>
<th>Risk Mitigation Strategies</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal Side Effects</td>
<td>SGAs or low-potency FGAs</td>
<td>B</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>SGA</td>
<td>B</td>
</tr>
<tr>
<td>Sedation</td>
<td>Haloperidol or paliperidone</td>
<td>B</td>
</tr>
<tr>
<td>Weight gain on antipsychotic medications</td>
<td>Haloperidol or ziprasidone</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Lifestyle interventions</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
<td>B</td>
</tr>
</tbody>
</table>

References:
4. Leucht S et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet. 382 (9896); 951-936.
5. AAAC Rate Listing for Brand and Generic Drugs. Available at http://or.mslc.com/AACRateArchive.aspx
Appendix B. Data Specification for Adherence to Antipsychotic Medications for Individuals With Schizophrenia (SAA) Modified

**Description**

The percentage of members 19–64 years of age during the measurement year with schizophrenia who were dispensed and remained on an antipsychotic medication for at least 80% of their treatment period.

<table>
<thead>
<tr>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPSD</strong></td>
</tr>
<tr>
<td><strong>Treatment period</strong></td>
</tr>
<tr>
<td><strong>PDC</strong></td>
</tr>
<tr>
<td><strong>Oral medication dispensing event</strong></td>
</tr>
<tr>
<td><strong>Long-acting injections dispensing event</strong></td>
</tr>
<tr>
<td><strong>Calculating number of days covered for oral medications</strong></td>
</tr>
</tbody>
</table>
Definitions

Calculating number of days covered for long-acting injections

Calculate number of days covered (for the numerator) for long-acting injections using the days-supply specified for the medication in Table B1. For multiple J Codes or NDCs for the same or different medications on the same day, use the medication with the longest days supply. For multiple J Codes or NDCs for the same or different medications on different days with overlapping days supply, count each day within the treatment period only once toward the numerator.

Eligible Population

Product lines

Medicaid.

Ages

19–64 years of age as of December 31 of the measurement year.

Continuous enrollment

The measurement year.

Allowable gap

No more than one gap in enrollment of up to 45 days during the measurement year. To determine continuous enrollment for a Medicaid beneficiary for whom enrollment is verified monthly, the member may not have more than a 1-month gap in coverage (i.e., a member whose coverage lapses for 2 months [60 days] is not considered continuously enrolled).

A manual review of gaps for all Oregon Medicaid members with less than 45 day without coverage found that all were single episode of loss of coverage. There were no members with multiple gaps. Therefore, simply use the total days of gap rather than instances and days.

Anchor date

December 31 of the measurement year.

Benefits

Medical and pharmacy.

Event/diagnosis

Follow the steps below to identify the eligible population.

Step 1

Identify members with schizophrenia as those who met at least one of the following criteria during the measurement year.

- At least one acute inpatient claim/encounter (Table B2) with any diagnosis of schizophrenia (ICD9 295).
- At least two visits in an outpatient, intensive outpatient, partial hospitalization, ED or nonacute inpatient setting (Table B2) on different dates of service, with any diagnosis of schizophrenia (ICD9 295).

Step 2: Required exclusions

Members with a diagnosis of dementia (Table B3) during the measurement year.

Members who did not have at least two antipsychotic medication (Table B1) dispensing events during the measurement year.
# Table B1: Antipsychotic Medications

<table>
<thead>
<tr>
<th>Description</th>
<th>Prescription</th>
<th>J Codes</th>
<th>Covered Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscellaneous antipsychotic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td></td>
<td>Paliperidone</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>Quetiapine fumarate</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td></td>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td></td>
<td>Ziprasidone</td>
<td></td>
</tr>
<tr>
<td>Lurisadone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molindone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenothiazine antipsychotics</td>
<td></td>
<td>Chlorpromazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluphenazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perphenazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trifluoperazine</td>
<td></td>
</tr>
<tr>
<td>Psychotherapeutic combinations</td>
<td></td>
<td>Fluoxetine-olanzapine</td>
<td></td>
</tr>
<tr>
<td>Thioxanthenes</td>
<td></td>
<td>Thiothixene</td>
<td></td>
</tr>
<tr>
<td>Long-acting injections</td>
<td></td>
<td>Aripiprazole</td>
<td>28 days supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paliperidone-palmitate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>J0400 (aripiprazole)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>J1631 (haloperidol decanoate),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>J2358 (olanzapine),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>J2426 (Paliperidone palmitate),</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td>J2680 (fluphenazine decanoate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>J2794 (risperidone microspheres)</td>
<td>14 days supply</td>
</tr>
</tbody>
</table>

Exclude J code claims without NDCs and with incorrect NDCs. A manual review of claims indicated that immediate release antipsychotic NDCs were used for the long acting injectable J code. Including these claims would artificially inflate the adherence rate. Likewise, J Code claims without NDCs may not have administered the long acting agent and are therefore excluded. For risperidone dispensed at the pharmacy, the number of units dispensed is evaluated to determine the length of therapy. If one unit is dispensed, the duration is calculated as 14 days. For prescriptions with 2 units dispensed, the duration of coverage is assumed to be 28 days.

## Administrative Specification

<table>
<thead>
<tr>
<th>Denominator</th>
<th>The eligible population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerator</td>
<td>The number of members who achieved a PDC of at least 80% for their antipsychotic medications (Table B1) during the measurement year.</td>
</tr>
</tbody>
</table>

Follow the steps below to identify numerator compliance.

**Step 1** Identify the IPSD. The IPSD is the earliest dispensing event for any antipsychotic medication (Table B1) during the measurement year.

**Step 2** To determine the treatment period, calculate the number of days from the IPSD (inclusive) to the end of the measurement year.

**Step 3** Count the days covered by at least one antipsychotic medications (Table B1) during the treatment period. To ensure that the days supply does not exceed the treatment period, subtract any days supply that extends beyond December 31 of the measurement year.

**Step 4** Calculate the member’s PDC using the following equation.

\[
\text{Total Days Covered by an Antipsychotic Medication in the Treatment Period (step 3)}
\]

\[
\text{Total Days in Treatment Period (step 2)}
\]

**Step 5** Sum the number of members whose PDC is ≥80% for their treatment period.
# Table B2: Codes to Identify Visit Type

<table>
<thead>
<tr>
<th>Description</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inpatient</td>
<td>010x, 0110-0114, 0119, 0120-0124, 0129, 0130-0134, 0139, 0140-0144, 0149, 0150-0154, 0159, 016x, 020x, 021x, 072x, 0987</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>POS</th>
</tr>
</thead>
<tbody>
<tr>
<td>90801, 90802, 90816-90819, 90821-90824, 90826-90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870, 90875, 90876, 99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291</td>
<td>21, 51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>HCPCS</th>
<th>UB Revenue</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>POS</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>90801, 90802, 90816-90819, 90821-90824, 90826-90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870, 90875, 90876, 99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291</td>
<td>03, 05, 07, 09, 11, 12, 13, 14, 15, 20, 22, 24, 33, 49, 50, 52, 53, 71, 72</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>90281-90285</td>
<td>045x, 0981</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>POS</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>90801, 90802, 90816-90819, 90821-90824, 90826-90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870, 90875, 90876, 99291</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>HCPCS</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>99304-99310, 99315, 99316, 99318, 99324-99328, 99334-99337</td>
<td>H0017-H0019, T2048</td>
<td>0118, 0128, 0138, 0148, 0158, 019x, 0524, 0525, 055x, 066x, 1000, 1001, 1003-1005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT</th>
<th>POS</th>
<th>UB Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>90801, 90802, 90816-90819, 90821-90824, 90826-90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870, 90875, 90876, 99291</td>
<td>31, 32, 56</td>
<td></td>
</tr>
</tbody>
</table>

# Table B3: Codes to Identify Dementia

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>290, 291.2, 292.82, 294.0-294.2, 331.0, 331.1, 331.82</td>
</tr>
</tbody>
</table>

# Table B4: Codes to Identify Substance Abuse

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis</th>
</tr>
</thead>
</table>
OHP Zolpidem Drug Use Evaluation

**Background:** Evidence-based treatment guidelines recommend behavioral interventions directed at improving sleep hygiene as first-line treatment based upon moderate level evidence. Benzodiazepine and non-benzodiazepine sedative-hypnotics alike appear to reduce sleep latency and moderately increase total sleep time in chronic insomnia based upon moderate level evidence but do so with an increased risk of “complex sleep-related behaviors including sleep-driving, impaired psychomotor performance (which may contribute to falls and hip fracture), anaphylaxis, angioedema, and abuse potential” according to United States Food & Drug Administration (FDA) warnings. The FDA required label changes in May 2013 warning that zolpidem impaired patients the next morning and recommended that lower doses be used initially (i.e. 5/6.25mg for women and 10/12.5 mg for men).

Medical treatment of disorders of sleep in the absence of sleep apnea is a non-funded condition on the Oregon Health Plan prioritized list (Line: 636). The Oregon Health Plan (OHP) fee-for-service (FFS) program requires prior authorization of benzodiazepine sedative-hypnotics for more than 15 doses per month to insure a funded diagnosis (i.e. comorbid disease such as bipolar disease or depression). Non-benzodiazepine sedative-hypnotics, with the exception of generic zolpidem oral tablets, are also prior authorized for funded diagnosis and limited to 15 doses per month. Concurrent claims for sedative-hypnotics require prior authorization.

The goal of this drug use evaluation is to determine the extent of long-term use of zolpidem oral tablets and the extent of daily dose in excess of FDA labeling in the OHP FFS population for zolpidem tablets in comparison to all other sedative-hypnotics.

**Methods:**

Patients with a paid FFS drug claim for a sedative-hypnotic (Appendix A) with a service date from July 1, 2012 thru June 30, 2013 were analyzed. Patients were excluded if they were covered by Medicare as defined by benefit packages (BMM or BMD) or had <75% of days of FFS OHP eligibility of in study period.

Patients were included in the study group if they had a paid claim for zolpidem oral tablets. Patients were included in the control group if they had a paid claim for a sedative-hypnotic and no claims for zolpidem oral tablets. All sedative-hypnotics claims were analyzed in combination per patient for study outcomes.

**Therapy Length** was determined using the date of the first claim in the study period for a sedative-hypnotic with a minimum **Day’s Supply** of 5 days. The minimum **Day’s Supply** is set to exclude outliers due to inaccurate data entry. A continuous therapy span was determined by summing the **Day’s Supply** of all subsequent claims where the fill date did not exceed the previous claim’s **Day’s Supply** by more than 15 days. All sedative-hypnotic claims were combined for the therapy length determination. The longest therapy span was used to calculate **Therapy Length** for patients with more than one span. The number of patients on short-term therapy (less than or equal to 30 days) and the number of patients on long-term therapy (greater than 30 days) were reported.

**Daily Consumption** for all sedative-hypnotics for a patient was calculated by summing the **Quantity Dispensed** divided by the summed **Day’s Supply for a Therapy Length**. **Daily Consumption** less than or equal to 0.5 units (e.g. tablets) per day is within the current policy limits and indicates non-continuous use (i.e. 1 unit every other day). **Daily Consumption**
greater than 0.5 units per day exceeds the current policy limits. The number of patients exceeding or meeting the current policy limits for Daily Consumption were reported for patients on short- and long-term therapy.

The number of patients exceeding the FDA recommended initial dose for each drug product was determined for patients with more than 1 claim with a Day’s Supply greater than 5 days. For the patients meeting the minimum criteria, the Daily Consumption was calculated by summing the Quantity Dispensed dividing by the summed Day’s Supply for all claims for that drug product. The number of patients exceeding 1 unit per day was reported as exceeding the recommended initial dose.

Results:
Less than half of patients with a sedative-hypnotic claim met the inclusion criteria (Table 1). Control patients were primarily excluded for Medicare coverage and most study patients did not remain in FFS for 75% of the days in the study period.

Table 1 - Exclusion Flowchart

<table>
<thead>
<tr>
<th>Patients with Any Sedative Hypnotic</th>
<th>Total n</th>
<th>Excluded</th>
<th>Control n</th>
<th>Excluded</th>
<th>Study n</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with FFS claim</td>
<td>1,537</td>
<td></td>
<td>345</td>
<td>188</td>
<td>1,192</td>
<td>1,180</td>
</tr>
<tr>
<td>Excluded Medicare</td>
<td>1,368</td>
<td>169</td>
<td>157</td>
<td></td>
<td>1,180</td>
<td>12</td>
</tr>
<tr>
<td>Exclude &lt;75% eligibility</td>
<td>621</td>
<td>747</td>
<td>101</td>
<td>87</td>
<td>520</td>
<td>660</td>
</tr>
</tbody>
</table>

The study group is 5 times larger than the control group (Table 2). However, the demographics are similar with only significant difference the increased prevalence of teenagers and children in the control group. Caucasian (84%), women (69-72%) are predominate sedative-hypnotic users.

Table 2: Demographics

Notes: Control group includes any patient on a sedative hypnotic, but with no claims for oral zolpidem. Study group includes any patient with a claim for oral zolpidem

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 101</td>
<td>%</td>
<td>n= 520</td>
<td>%</td>
</tr>
<tr>
<td>Age on day of index claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Min - Max)</td>
<td>37.3 (5-63)</td>
<td>42.3 (8-67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 13</td>
<td>4</td>
<td>4.0%</td>
<td>7</td>
<td>1.3%</td>
</tr>
<tr>
<td>13-18</td>
<td>14</td>
<td>13.9%</td>
<td>28</td>
<td>5.4%</td>
</tr>
<tr>
<td>19-64</td>
<td>83</td>
<td>82.2%</td>
<td>481</td>
<td>92.5%</td>
</tr>
<tr>
<td>&gt; 64</td>
<td>0</td>
<td>-</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>31</td>
<td>30.7%</td>
<td>148</td>
<td>28.5%</td>
</tr>
<tr>
<td>F</td>
<td>70</td>
<td>69.3%</td>
<td>372</td>
<td>71.5%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>85</td>
<td>84.2%</td>
<td>433</td>
<td>83.3%</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>16</td>
<td>15.8%</td>
<td>87</td>
<td>16.7%</td>
</tr>
</tbody>
</table>
Table 3 displays that more of the study group met the criteria for sustained use (496/520 = 95%) than the control group (65/101 = 64%). Sustained use was defined as a minimum day *Day’s Supply* of 5 days to exclude claims more likely to include data entry errors that would affect *Daily Consumption* calculations and very short courses of therapy.

**Table 3: Drug Use Description**

*Notes: Treatment length is defined as each patient’s longest span of sustained therapy for all sedative hypnotics combined. Sustained therapy defined as a minimum of 5 days supply with gap between claims not to exceed 15 days. If at any point the patient had oral zolpidem, they are counted in Study population, regardless of presence of other sedative hypnotic agents. Daily Consumption is calculated by patient from only the claims related to their longest span of sustained therapy.*

<table>
<thead>
<tr>
<th>Therapy Length in Days</th>
<th>Control</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 101</td>
<td>%</td>
</tr>
<tr>
<td># Patients &gt; 30 days</td>
<td>44</td>
<td>43.6%</td>
</tr>
<tr>
<td># Patients &gt; 5 days and ≤ 30 days</td>
<td>21</td>
<td>20.8%</td>
</tr>
<tr>
<td># Patients &lt; 5 days</td>
<td>37</td>
<td>36.6%</td>
</tr>
</tbody>
</table>

| Patients on sustained therapy (> 5 days) | n=65 | 64% | n=496 | 95% |
| Daily Consumption (DaCon) (Quantity Dispensed / Day’s Supply) | | | |
| # Patients > 0.5 x > 30 days | 43 | 66.2% | 308 | 62.1% |
| # Patients > 0.5 x ≤ 30 days | 19 | 29.2% | 166 | 33.5% |
| # Patients ≤ 0.5 x > 30 days | 1 | 1.5% | 13 | 2.6% |
| # Patients ≤ 0.5 x ≤ 30 days | 2 | 3.1% | 9 | 1.8% |

The absolute numbers for control patients exceeding the FDA recommended dose of 1 unit per day (Table 4) are too low to reliably interpret. Study patients exceeded the FDA recommendations in 26% of patients using the 5 mg strength of zolpidem and in 10% of patients using the 10mg strength. Not included in Table 4, 26% of women using the 5 mg strength of zolpidem and 12% of men and 9% of women using the 10mg strength. In fact, 206 of the 295 patients (70%) on zolpidem 10mg were women, all of which are exceeding the new FDA recommended dose for women.
### Table 4: Patients with Average Dose Exceeding FDA Recommendation (i.e. > 1 tablet/day)

*Notes: Table 3 dose is not based on continuous treatment length. It simply finds the average Daily Consumption per patient per agent, for all claims during study period. For each agent, only those patients with more than one claim are included, and only those claims with Day’s Supply > 5 days are counted.*

<table>
<thead>
<tr>
<th>GSN</th>
<th>Generic Drug Name</th>
<th>Str</th>
<th>Form</th>
<th>Patients with &gt;1 claim &amp; DaSup &gt; 5 n=</th>
<th>Patients with Average DaCon &gt;1 n=</th>
<th>% DaCon &gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>066591</td>
<td>DOXEPIN HCL</td>
<td>3 mg</td>
<td>TABLET</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>015603</td>
<td>ESTAZOLAM</td>
<td>1 mg</td>
<td>TABLET</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
</tr>
<tr>
<td>058484</td>
<td>ESZOPICLONE</td>
<td>1 mg</td>
<td>TABLET</td>
<td>2</td>
<td>1</td>
<td>50.0%</td>
</tr>
<tr>
<td>058483</td>
<td>ESZOPICLONE</td>
<td>2 mg</td>
<td>TABLET</td>
<td>7</td>
<td>1</td>
<td>14.3%</td>
</tr>
<tr>
<td>058482</td>
<td>ESZOPICLONE</td>
<td>3 mg</td>
<td>TABLET</td>
<td>7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>059509</td>
<td>RAMELTEON</td>
<td>8 mg</td>
<td>TABLET</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>019182</td>
<td>TEMAZEPAM</td>
<td>7.5 mg</td>
<td>CAPSULE</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
</tr>
<tr>
<td>003689</td>
<td>TEMAZEPAM</td>
<td>15 mg</td>
<td>CAPSULE</td>
<td>11</td>
<td>2</td>
<td>18.2%</td>
</tr>
<tr>
<td>003690</td>
<td>TEMAZEPAM</td>
<td>30 mg</td>
<td>CAPSULE</td>
<td>4</td>
<td>2</td>
<td>50.0%</td>
</tr>
<tr>
<td>003693</td>
<td>TRIAZOLAM</td>
<td>0.125 mg</td>
<td>TABLET</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>003694</td>
<td>TRIAZOLAM</td>
<td>0.25 mg</td>
<td>TABLET</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>042993</td>
<td>ZALEPLON</td>
<td>5 mg</td>
<td>CAPSULE</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>042994</td>
<td>ZALEPLON</td>
<td>10 mg</td>
<td>CAPSULE</td>
<td>2</td>
<td>1</td>
<td>50.0%</td>
</tr>
<tr>
<td>059696</td>
<td>ZOLPIDEM TARTRATE</td>
<td>6.25 mg</td>
<td>TAB MPHASE</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
</tr>
<tr>
<td>059697</td>
<td>ZOLPIDEM TARTRATE</td>
<td>12.5 mg</td>
<td>TAB MPHASE</td>
<td>19</td>
<td>3</td>
<td>15.8%</td>
</tr>
<tr>
<td>019187</td>
<td>ZOLPIDEM TARTRATE</td>
<td>5 mg</td>
<td>TABLET</td>
<td>84</td>
<td>22</td>
<td>26.2%</td>
</tr>
<tr>
<td>019188</td>
<td>ZOLPIDEM TARTRATE</td>
<td>10 mg</td>
<td>TABLET</td>
<td>295</td>
<td>29</td>
<td>9.8%</td>
</tr>
</tbody>
</table>
Discussion:

Current OHP FFS policy allows open access to generic zolpidem tablets to provide an alternative to therapies (i.e. low dose quetiapine, trazadone and diphenhydramine) with lower evidence for efficacy for insomnia. Insomnia treatment is funded when co-morbid with mental health conditions (i.e. bipolar disease, anxiety and depression). The study group is 5 times larger than the control group, likely due to the open access to zolpidem. More study group patients were on sustained therapy longer than 30 days (62%) compared to the control group (44%). Additionally, 26% of female patients on zolpidem 5mg and 10% of all patients on zolpidem 10mg exceed the FDA recommended dose for safety (i.e. > 1 unit / day). This is particularly concerning for women where 290/295 (70%) of the patients prescribed the 10mg dose were women and the recommended dose is 5 mg.

The control group excluded a significant number of Medicare patients likely because the control group includes benzodiazepine sedative-hypnotics which were being transitioned from Medicaid to Medicare coverage during the study period. The primary source of exclusions from the study group was patients not remaining in FFS for 75% of the study period. While the exclusion criteria affected the populations differently, the remaining population was similar in demographics except that children comprised a somewhat higher prevalence in the control population which could skew the Daily Consumption for the control group downward somewhat. However, there is not significant evidence of this.

Recommendation:

1) Limit zolpidem Daily Consumption to 0.5 units per day (i.e. 15 units / 30 days) by prior authorization to discourage continuous daily use.

2) Place a prior authorization for women on zolpidem 10mg and 12.5mg.
REFERENCES:


**APPENDIX A:** Sedative-Hypnotics are listed below with study drugs in bold.

<table>
<thead>
<tr>
<th>HSN</th>
<th>Generic Drug Name</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1592</td>
<td>TEMAZEPAM</td>
<td>CA - CAPSULE</td>
</tr>
<tr>
<td>1593</td>
<td>FLURAZEPAM HCL</td>
<td>CA - CAPSULE</td>
</tr>
<tr>
<td>1594</td>
<td>TRIAZOLAM</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>1595</td>
<td>QUAZEPAM</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>1650</td>
<td>DOXEPIN HCL</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>20347</td>
<td>ZALEPLON</td>
<td>CA - CAPSULE</td>
</tr>
<tr>
<td>26791</td>
<td>ESZOPICLONE</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>33126</td>
<td>RAMELTEON</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>6036</td>
<td>ESTAZOLAM</td>
<td>TA - TABLET</td>
</tr>
<tr>
<td>7842</td>
<td>ZOLPIDEM TARTRATE</td>
<td>UB - TAB MPHASE</td>
</tr>
<tr>
<td>7842</td>
<td>ZOLPIDEM TARTRATE</td>
<td>TU - TAB SUBL</td>
</tr>
<tr>
<td><strong>7842</strong></td>
<td><strong>ZOLPIDEM TARTRATE</strong></td>
<td><strong>TA - TABLET</strong></td>
</tr>
</tbody>
</table>
Abbreviated Class Review: Immunoglobulin G

Month/Year of Review: March 2014
End date of literature search: January 1, 2014
Current PDL Class: None

Research Questions:
• What is the comparative efficacy of the different dosage forms of immunoglobulin G?
• What are the comparative safety differences between the different forms of immunoglobulin G?
• Are there certain subpopulations that benefit from a specific dosage form of immunoglobulin G?

Conclusions:
• There is robust evidence to support the use of intravenous immunoglobulin G (IVIG) for primary immunodeficiency. This route of administration allows a large volume per infusion, and is administered relatively infrequently (every three to four weeks), however it must be administered by a trained professional, venous access is required, and it is associated with greater fluctuations in IgG levels, potentially resulting in a greater incidence of adverse effects.  
• There is robust evidence to support the use of subcutaneous IgG (SCIG) for primary immunodeficiency. This formulation may be appealing to patients due to a lack of requirement of venous access, a perceived sense of independence associated with self-administration, and more consistent serum IgG levels. Limitations of SCIG include increased dosing frequency, requirement of multiple dosing sites, and the need for competent and adherent patients.
• There is no strong evidence that indicates a preferential route of administration of IgG. Systematic reviews and cross-trial comparisons indicate that there is no difference in efficacy between IVIG and SCIG products. Products with low IgA counts may be preferable to those who experience infusion reactions.
• There is no strong evidence that shows that the differences in the pharmacokinetic profiles of IVIG and SCIG translate to meaningful improvements in patient outcomes. While some studies showed a lower incidence of adverse events in SCIG versus IVIG, the 20% SCIG formulation has not been directly compared to IVIG.

Recommendations:
• IVIG products are similar in efficacy and should be prescribed based on the risk of adverse events with each formulation, cost, and history of IVIG use.
• The choice of IVIG or SCIG should account for the individual patient’s ability to administer IgG at home, compliance, availability and ease of IV access, and comorbid conditions.

Reason for Review:
The availability of a concentrated SCIG product has revived the question of the optimal administration of IgG therapy. This review will evaluate different IgG products and routes of infusion for products currently available in the United States.
Background:
Primary immunodeficiency (PI) is a group of more than 150 genetically determined conditions that leaves those affected susceptible to frequent infections.\(^1\) PIs are distinct from secondary immunodeficiencies, which result from other causes including malnutrition, immunosuppressant drugs and infections.\(^2\) The prevalence of PI in the United States is estimated to be 1/1,200 persons, which results in an estimated 250,000 cases.\(^3\) Most PI disorders present early in childhood, but can present at any time throughout life.\(^4\) Immunologists typically diagnose PI via a comprehensive immune evaluation that initially involves a complete blood count and blood smear.\(^2\) PI can be fatal if patients contract infections that are not or cannot be treated.

Treatment for PI involves management of existing infections, IgG replacement therapy (often indefinitely), and antibiotic and antifungal prophylaxis to reduce frequency and severity of infections.\(^2\) While IgA and IgM have been studied for immunodeficiencies, IgG is the only product approved for treating PI. Due to the long serum half-life, IgG infusion is typically administered every 2-4 weeks. A nationwide survey of patients showed that 83% of PI patients report receiving regular infusion of IgG.\(^1\) IgG products are created by pooling IgG from 2,000 to 10,000 human donors and vary in their concentration, amount of IgA, pH, stabilizer, storage requirements, and sucrose content.\(^5\) There is no general consensus on the appropriate dosing of IgG. Studies have shown that an individualized approach to IgG dosing should be done that factors in both serum levels and infections.\(^5\)

IgG can be infused intravenously (IV), intramuscularly (IM), or subcutaneously (SC), however no IM formulations of IgG are available in the United States.\(^6\) While immunoglobulin that is administered intravenously (IVIG) remains the most commonly used product, subcutaneous (SCIG) administration is gaining popularity due to availability of new SC products, which provide a lack of need for venous access and opportunity for in-home administration. Theoretically, the pharmacokinetic profile of SCIG results in fewer adverse events than IVIG formulations, because the peaks and nadirs are closer and more stabilized due to slow absorption and increased frequency of administration.

Table 1. Indications and Dosing of IgG Products

<table>
<thead>
<tr>
<th>Brand Name (Manufacturer)</th>
<th>INDICATIONS</th>
<th>STRENGTH/ROUTE</th>
<th>DOSE AND FREQUENCY:</th>
<th>INFUSION RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammunex-C (^{7}) Kedrion (Grifols)</td>
<td>PI, IT, CIDP</td>
<td>10%/IV or SC</td>
<td>PI, IV: 300-600 mg/kg every 3-4 weeks Pl, SC: (1.3xIV dose)/(IV interval) IT: 2g/kg CIDP: 2g/kg (LD), 1g/kg (MD), every 3 weeks</td>
<td>PI, IV: 0.5-1.8mg/kg/min Pl, SC: 0.2-0.3mg/kg/min IT: 0.1-0.3mg/kg/min CIDP: 0.2-0.3mg/kg/min</td>
</tr>
<tr>
<td>Gammaked (^{8})</td>
<td>PI, IT, CIDP</td>
<td>10%/IV</td>
<td>PI, IV: 300-600 mg/kg every 3-4 weeks Pl, SC: (1.3xIV dose)/(IV interval) IT: 2g/kg CIDP: 2g/kg (LD), 1g/kg (MD), every 3 weeks</td>
<td>PI, IV: 0.5-1.8mg/kg/min Pl, SC: 0.2-0.3mg/kg/min IT: 0.1-0.3mg/kg/min CIDP: 0.2-0.3mg/kg/min</td>
</tr>
<tr>
<td>Octagam (^{9}) (Octapharma)</td>
<td>PI</td>
<td>5%/IV</td>
<td>300-600mg/kg every 3-4 weeks</td>
<td>0.5 – 3.33 mg/kg/min</td>
</tr>
<tr>
<td>Bivigam (^{10}) (Biotest)</td>
<td>PI</td>
<td>10%/IV</td>
<td>300-800mg/kg every 3-4 weeks</td>
<td>0.5 – 6mg/kg/min</td>
</tr>
<tr>
<td>Gammaplex (^{11}) (Bio Products Laboratory)</td>
<td>PI, IT</td>
<td>5%/IV</td>
<td>PI: 300-800mg/kg every 3-4 weeks IT: 1g/kg x 2 days</td>
<td>0.5 - 4mg/kg/min (PI and IT)</td>
</tr>
<tr>
<td>Gammagard Liquid (^{12}) (Baxter)</td>
<td>PI, MMN</td>
<td>10%/IV or 10% SC</td>
<td>PI, IV: 300-600mg/kg every 3-4 weeks Pl, SC: (1.3xIV dose)/(IV interval) MMN, IV: 0.5-2.4g/kg/month</td>
<td>PI, IV: 0.5-5.4mg/kg/hr Pl, SC: ≥40kg: 30mL/site at 20-30 mL/hr/site &lt;40kg: 20mL/site at 15-20mL/hr/site MMN: Up to 5.4mL/kg/hr</td>
</tr>
</tbody>
</table>
Methods:
A Medline literature search ending January 2014 for new systematic reviews and randomized controlled trials (RCT’s) comparing IgG products for the treatment of primary immunodeficiency. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Efficacy of IVIG and SCIG in Primary Immunodeficiency
There are no head to head studies comparing concentrated SCIG to IVIG in PI. Although immune globulin has been used since the 1950’s to treat patients with PI, a 1997 shortage prompted the Food and Drug Administration (FDA) to review and adjust guidelines for the IVIG new drug approval process, which included standardizing the clinical trials used to establish efficacy and safety of new IVIG products. After difficulty recruiting patients with this rare disease, the FDA again revised their standards for IVIG clinical trials, and proposed single-arm, 12-month, open-label studies including about 50 patients as an acceptable trial design for studying IVIG products. The desired primary endpoint was determined to be the rate of acute serious bacterial infections (SBIs), which includes bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. Using results from historical trials, the FDA established the target SBI rate at <1.0 per subject per year at the 0.01 level of significance.

Recent clinical trials evaluating the efficacy of IVIG include between 46 and 73 patients with PI. Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) were the two most common types of PI studied. Gamunex and Gammimune N were evaluated in a prospective, randomized, double-blind, non-inferiority study. Octagam, Gammagard, Privigen, Flebogamma, Gammamix, and Bivigam were all studied using the FDA recommended trial design of open-label, historically controlled, single-arm trials. The rate of SBIs was well below the target of <1.0 SBI/person/year, ranging from 0 to 0.08 SBI/person/year among the various products. The rate of non-serious infections varied from 1.96-3.55 infections/person/year. The rate of adverse events was variable between studies. Studies that reported out treatment-related adverse events as a percent of infusions showed rates from 5% -27.6% depending on the product. The most common adverse event reported in each study was headache.

Concentrated SCIG was studied in a prospective, open-label, multicenter, single-arm, phase 3 study. The study included patients who had previously been treated with IVIG and used an SCIG dose that was equivalent to the IVIG dose, as measured by the area under the concentration/time curve (AUC) of serum IgG. The study included a 12-week wash-in/wash-out period followed by a 12-month efficacy period. The primary efficacy end point of SBIs per patient was
0, exceeding the FDA’s target. The safety profile of Hizentra 20% was similar to other IgG products in nature and in frequency. The overall rate of infusion-related AEs was 0.043 per infusion, and the most common adverse events were headache, fatigue, and nausea.\(^{17}\) Results from this phase 3 trial aligned with that of another open-label, single-arm study (n=51), which found that 0 SBIs occurred after 40 weeks of treatment with Hizentra 20%. This study used a dose of Hizentra 20% that was equivalent to the subject’s previous IVIG dose, measured by the trough IgG levels, in accordance with guidelines from the European Medicines Agency.\(^{18}\)

A small comparative study (n=13) was completed in pediatric patients with PI in Argentina. In the observational, retrospective/prospective, open-label study, patients previously treated with IVIG for at least 12 months received SCIG (16%) for 26 weeks. The primary efficacy endpoints were the serum IgG trough level and the number of SBIs, which was defined using the FDA’s criteria. There were no SBIs during the retrospective and prospective phases of the study. The rate of any infection was 0.4 infections/patient/year during the SCIG phase and 1.4 infections/patient/year during the IVIG phase. No serious adverse events were reported. During the IVIG phase, there were 0.08 events/infusion, most of which were headaches. During the SCIG phase, there were 0.14 events per infusion, however it should be noted that three subjects reported 88% of all adverse events. All adverse events were mild local infusion site reactions.\(^{19}\)

| Table 2. Summary of Pivotal Studies Completed in Patients with Primary Immunodeficiency |
|---------------------------------|----------------|----------------|----------------|----------------|
| Treatment                      | Population     | Outcome                    | Efficacy            | Safety                    | Trough IgG                |
| Gamunex 10%                    | • Mean age: 35.1 | Proportion of patients with at least one validated acute sinopulmonary infection | 12.3%               | TRAEs: 5.7% of infusions | Not reported |
| • 3 week: n=9                  | • CVID: 53%    |                                                                           |                      |                           |
| • 4 week: n=64                 | • Hypogam: 45% |                                                                           |                      |                           |
| Gammimune N                    | • Mean age: 29.5 |                                                                           | 23.3%               | TRAEs: 5.5% of infusions  |                           |
| • 3 week: n=14                 | • CVID: 52%    |                                                                           |                      |                           |
| • 4 week: n=59                 | • Hypogam: 41% |                                                                           |                      |                           |
| Octagam 5%                     | • Mean age: 31  | Rate of serious infections per patient per year                            | 0.1 serious infections/subject/year | TRAEs: 5% of infusions    |                           |
| • 3 week: n=19                 | • CVID: 61%    |                                                                           |                      |                           |
| • 4 week: n=27                 | • XLA: 28%     |                                                                           |                      |                           |
| Gammagard 10% n=61             | • Mean age: 34  | Rate of serious infections per patient per year                            | No serious infections were reported | SAEs: 2 aseptic meningitis episodes in 1 patient | 960-1,120 mg/dL |
| • CVID or hypogam: 67.2%       | • XLA: 17.4%   |                                                                           |                      |                           |
| Privigen 10%                   | • Mean age: 28  | Rate of serious infections per patient per year                            | 0.08 serious infections/subject/year | TRAEs: 9% of infusions    | 884-1,027 mg/dL |
| • 3 week: n=16                 | • CVID: 73.8%  |                                                                           |                      |                           |
| • 4 week: n=64                 | • XLA: 26.2%   |                                                                           |                      |                           |
| Flebogamma DIF 10%             | • Mean age: 36.8 | Rate of serious infections per patient per year                            | 0.025 serious infections/subject/year | TRAEs: 27.6% of infusions | Not reported |
| • 3 week: n=16                 | • CVID: 80.4%  |                                                                           |                      |                           |
| • 4 week: n=30                 | • XLA: 17.4%   |                                                                           |                      |                           |
| Gammaglide 5%                  | • Mean age: 44  | Rate of serious infections per patient per year                            | 0 serious infections/subject/year | TRAEs: 16.4% of infusions |                           |
| • 3 week: n=22                 | • CVID: 92%    |                                                                           |                      |                           |
| • 4 week: n=38                 | • XLA: 8%      |                                                                           |                      |                           |
| Bivigam 10%                    | • Mean age: 41.2 | Rate of serious infections per patient per year                            | 0.037 serious infections/subject/year | TRAEs: 63.5% of subjects |                           |
| • 3 week: n=17                 | • CVID: 81%    |                                                                           |                      |                           |
| • 4 week: n=46                 | • XLA: 9.5%    |                                                                           |                      |                           |
Hizentra 20%
\( n=49 \) (ITT)
\( n=38 \) (MITT)
- Mean age: 36.3
- CVID: 95%
- XLA: 5%

| Rate of serious infections per patient per year | 0 serious infections/subject/year (ITT and MITT) | TRAEs: 4.3% of infusions | 12.53 g/dL |

CVID: Common variable immunodeficiency; XLA: X-linked agammaglobulinemia; TRAE: Treatment-related adverse events; SAE: serious adverse event; ITT: intention to treat; MITT: modified intention to treat

RCT: randomized controlled trial, DB: double-blind, PG: parallel group

2. Systematic Reviews/Meta-analyses:
   a. Primary Immunodeficiency

A systematic review/meta-analysis evaluated home-based SCIG versus hospital-based IVIG in the treatment of primary antibody deficiencies. The literature search used a Cochrane Collaboration tool for assessing risk of bias, including method of randomization, allocation concealment, incomplete data addressed blinding of involved participants, free of selective reporting, groups comparable at baseline, sample size calculation and withdrawals or loss to follow up reports. Data outcomes from the collected trials were organized into five subclasses: (1) trough level and pharmacokinetics, (2) side effects and pre-medication, (3) efficacy, infection rate and hospitalization, (4) health related quality of life, treatment satisfaction and convenience, (5) missed days of work/school, and cost. The data was then analyzed with random effect analysis model and Mantel-Haenszel statistical method using Review Manager software (version 5.0). For continuous data inverse variance method and fixed effect analysis model were used and the mean difference was considered as an effect measure.\(^\text{20}\)

### Table 3. Summary of a Meta-analysis Comparing IVIG to SCIG\(^\text{20}\)

<table>
<thead>
<tr>
<th>Outcome (IgG trough levels)</th>
<th>Odds Ratio (OR)</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG trough levels (31; 1,059)</td>
<td>1.00</td>
<td>(0.84-1.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serious infection rate in patients who received IVIG versus SCIG (9; 269)</td>
<td>0.59</td>
<td>(0.36-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse events (15; 376)</td>
<td>0.09</td>
<td>(0.07-0.11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The initial data search found 156 titles, of which 79 met title review criteria. Of these, 47 (10 clinical trials, 17 prospective cohorts and 20 retrospective cohorts) met criteria and addressed at least one of the identified outcomes. These papers contained 1,484 of which 67.7% were adults, and 56.3% carried the diagnosis of common variable immunodeficiency. The results of the meta-analysis are summarized in table 3.\(^\text{20}\)

One of the measured outcomes was IgG trough levels, and the data showed that serum IgG trough levels were comparable between IVIG and SCIG formulations. The two measured outcomes of serious infection rate in patients who received IgG, and adverse effects, showed significant preference for SCIG over IVIG. Most articles that evaluated IgG trough levels directly compared SCIG to IVIG.\(^\text{20}\) Of the 31 trials included in the IgG trough level analysis, the range of study subjects was 3-262. One study found that the amount of IVIG (0.39 g/kg) or SCIG (0.37 g/kg) required to maintain adequate trough concentrations did not differ between routes.\(^\text{21}\) The studies evaluating serious infection rate ranged from 11-65 subjects. The difference in infection rate is difficult to differentiate due to variation in dosing and infusion rates among the studies. One report found that the mean duration of recorded infections was 78 days among IVIG subjects (95% CI: 18-125 days) and 58 days for SCIG subjects (95% CI: 22-83 days), but the difference was not statistically significant (p=0.212).\(^\text{22}\) Differences in antibiotic usage were inconsistent. One trial\(^\text{23}\) showed a 24.4% decrease in antibiotic use when subjects were switched from IVIG to SCIG. A second trial\(^\text{19}\) found a 28% increase in antibiotic use for subjects switched to SCIG. The trials that evaluated adverse effects enrolled 3-262

Author: B. Fouts, Pharm.D.
Overall, there were fewer adverse reactions with the SCIG formulation, however patients using the SCIG formulation at home may have been less likely to report adverse events than those being treated with IVIG at the hospital.20

3. Guidelines

The Immune Deficiency Foundation Guidelines
In 2011, the Immune Deficiency Foundation (IDF) published guidelines on diagnosis and clinical care for primary immunodeficiency diseases. The guidelines help clinicians determine the possible type of PI and the screening diagnostic tests that should be ordered based on the site of infection. While there are several different types of PI, the types that result in antibody production defects are those that are eligible for IgG therapy.5

The IDF recommends regular IgG therapy for patients with identified antibody deficiency disorders. The guidelines state the IVIG product should be dosed every 2-4 weeks and SCIG should be given every 1-14 days. It is recommended that an immunologist should participate in the determination of the proper dose and interval for IgG therapy in each patient. Doses of IgG generally range from 400-600 mg/kg of body weight. A goal trough IgG level should be >500 mg/dl for most patients, however clinical considerations of the individual patient should be considered when determining dose changes. Patients with infections at standard levels or with pulmonary infectious complications may want to target a higher trough of>800 mg/dl. The guidelines note that IgG therapy is considered a preventative therapy, and antibiotic should be used either prophylactically and/or for treatment of infections. Creatinine levels and liver function tests should be performed every 6-12 months while on IgG therapy. Should IgG treatment be required IV or SC administration are both recommended, and one product is not preferentially recommended over any other product.5

Canadian Blood Services and Canada’s National Advisory Committee Guidelines
The Canadian Blood Services and Canada’s National Advisory Committee on Blood and Blood Products led a joint initiative to create guidelines for treatment of PI with immunoglobulin therapy. While the guidelines are primarily intended for health care professionals in Canada, many of their recommendations may be applied in other parts of the world, including the United States.

The guidelines were constructed from an expert panel consisting of physicians from large pediatric and adult tertiary care centers who frequently cared for patients with primary immune deficiency, methodology experts, and members from the National Advisory Committee on Blood and Blood Products.24 The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care. The levels of evidence describe the methodological rigor of the study, and the grades of recommendation comprise the level of evidence and clinical expertise. Relevant recommendations include the following:

- Give immunoglobulin to patients with primary antibody deficiency to reduce infections. (Level of evidence: I, Grade of recommendation: A)
- Give immunoglobulin to reduce hospitalization and organ damage. (I, A)
- Give immunoglobulin to improve survival and quality of life. (III, A)
- With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products. (I to II-2, I)
- With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent. (I and II, B)
- When deciding on route of administration, patient preference should be taken into account. (III, A)
- Do not give IMIG for replacement therapy for primary immune deficiency. (I, D)
- Start IVIG at a dose of 400 to 600 mg/kg per 4 weeks or SCIG at a dose of 100 to 150 mg/kg per week in most patients. (III, B)
Patient and practitioners should be aware that patients with primary immune deficiency may require immunoglobulin replacement therapy indefinitely. (II-3, A)

A systematic review and one randomized controlled trial were used to evaluate the comparative efficacy and safety of IVIG and SCIG, and no statistically significant differences were found for severity and duration of infections. One report found that the patients treated with SCIG had a lower rate of infections (IVIG: 2.8 ± 2.0 infections/6 months; SCIG: 1.9 ± 1.9 infections/6 months), and two studies showed that SCIG was associated with improved quality of life. Studies were prospective and had small sample sizes. There were no statistically significant differences in trough levels.24
References:


Author: B. Fouts, Pharm.D.
Appendix 1: Specific Drug Information

Table 4. Product Descriptions

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>STORAGE</th>
<th>STABILIZER</th>
<th>IgA CONTENT</th>
<th>IgG PURITY</th>
<th>SODIUM CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammaked&lt;sup&gt;®&lt;/sup&gt;</td>
<td>36-46°F (2-8°C) for up to 36 months or 77°F (25°C) up to 6 months</td>
<td>Glycine</td>
<td>Average 0.046 mg/mL</td>
<td>≥98%</td>
<td>Not listed</td>
</tr>
<tr>
<td>Octagam&lt;sup&gt;®&lt;/sup&gt;</td>
<td>36-77°F (2-25°C) for up to 24 months</td>
<td>Maltose</td>
<td>≤0.2mg</td>
<td>≥96%</td>
<td>≤30mmol/l</td>
</tr>
<tr>
<td>Bivigam&lt;sup&gt;®&lt;/sup&gt;</td>
<td>36-46°F (2-8°C)</td>
<td>Glycine</td>
<td>≤0.2mg/mL</td>
<td>≥96%</td>
<td>0.1-0.140M</td>
</tr>
<tr>
<td>Gammagard Liquid&lt;sup&gt;®&lt;/sup&gt;</td>
<td>36-46°F (2-8°C) for up to 36 months or 77°F (25°C) up to 24 months</td>
<td>Glycine</td>
<td>Average 37mcg/mL</td>
<td>≥98%</td>
<td>No sodium</td>
</tr>
<tr>
<td>Carimune NF Nanofiltered&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Do not exceed 86°F (30°C)</td>
<td>Sucrose</td>
<td>Trace amounts</td>
<td>≥96%</td>
<td>20mg NaCl per gram of protein</td>
</tr>
<tr>
<td>Privigen&lt;sup&gt;®&lt;/sup&gt;</td>
<td>77°F (25°C) for up to 36 months</td>
<td>Proline</td>
<td>≤25 mcg/mL mg</td>
<td>≥98%</td>
<td>Trace amounts</td>
</tr>
<tr>
<td>Flebogamma Diff&lt;sup&gt;®&lt;/sup&gt;</td>
<td>36-77°F (2-25°C) for up to 24 months</td>
<td>Sorbitol</td>
<td>&lt;100 mcg/mL</td>
<td>≥97%</td>
<td>Trace amounts</td>
</tr>
<tr>
<td>Hizentra&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Room temperature (up to 77°F or 25°C) for up to 30 months.</td>
<td>Proline</td>
<td>≤50mcg/mL</td>
<td>≥98%</td>
<td>Trace amounts</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

All IVIG and SCIG products are pregnancy category C. Efficacy and safety of all products has not been evaluated.

Table 5. Summary of FDA Guidance in Pediatric and Geriatric Populations

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>PEDIATRIC USE</th>
<th>GERIATRIC USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammaked&lt;sup&gt;®&lt;/sup&gt;</td>
<td>PI, IV: Efficacy and safety similar to those in adults (n=18, age 0-16 years).</td>
<td>Use with caution</td>
</tr>
<tr>
<td></td>
<td>PI, SC: Not established</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITP: Efficacy and safety similar to those in adults (n=12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIDP: Not established</td>
<td></td>
</tr>
<tr>
<td>Octagam&lt;sup&gt;®&lt;/sup&gt;</td>
<td>No obvious differences in efficacy and safety compared to adults (n=11, age 6-16)</td>
<td>May be at increased risk for certain adverse reactions. Studied in 4 patients &gt;65 years old</td>
</tr>
<tr>
<td>Bivigam&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Efficacy and safety not established</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Gammagard Liquid&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Population too small to evaluate efficacy and safety</td>
<td>Population too small to evaluate efficacy and safety</td>
</tr>
</tbody>
</table>

Author: B. Fouts, Pharm.D.
### Gammagard Liquid

- **MMN**: Not studied
- **PI, IV**: Evaluated in 15 subjects ages 2-16
- **PI, SC**: Evaluated in 18 subjects ages 2-16.

Efficacy and safety were similar to those of adults.

- **PI**: Studied in 8 subjects >65. No differences in efficacy or safety were observed.
- **MMN**: Population too small to evaluate efficacy and safety

### Carimune NF Nanofiltered

- **PI**: Evaluated in 31 pediatric subjects. No apparent differences in efficacy and safety compared to adults.
- **ITP**: Not established in patients <15 years old.

Population too small to evaluate efficacy and safety.

### Privigen

- **PI**: Evaluated in 31 pediatric subjects.

Population too small to evaluate efficacy and safety.

Use with caution.

### Flebogamma Dif

Population too small to evaluate efficacy and safety.

### Hizentra

Safety and efficacy established in patients 2-16 years old.

Studied in 6 subjects ≥65 years old. No differences in efficacy or safety were observed.

### DRUG SAFETY

#### Black Box Warnings

- Thrombosis may occur with immune globulin products. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. For patients at risk of thrombosis, administer the immune globulin at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

- IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. For patients at risk of renal dysfunction or failure, administer immune globulin at the minimum concentration available and the minimum infusion rate practicable. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose. Cariumune NF contains sucrose, the other products included in this review do not. Hizentra does not carry this warning.

#### Contraindications

- Immune globulin products are contraindicated in patients with anaphylactic or severe systemic reaction to human immune globulin or components of the product.
- Immune globulin product are contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity.
- Octagam is contraindicated in patients with acute hypersensitivity reaction to corn.
- Gammaplex and Flebogamma are contraindicated in those with intolerance to any component of the product (i.e., intolerance to fructose). Gammaplex is also contraindicated in infants and neonates for whom sucrose or fructose tolerance has not been established.
- If patients are known to be intolerant to any component of Flebogamma, such as sorbitol (i.e., intolerance to fructose), they should not receive the product.
- Privigen and Hizentra are contraindicated in patients with hyperprolinemia.
Table 6. Summary of Warnings and Precautions for IgG Products

<table>
<thead>
<tr>
<th>Warning</th>
<th>Gammaked/ Gamunex-C A</th>
<th>Octagam 9</th>
<th>Bivigam 10</th>
<th>Gammaplex 11</th>
<th>Gammagard 12</th>
<th>Carimune 13</th>
<th>Privigen 14</th>
<th>Flebogamma-DIF 15</th>
<th>Hizentra 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitive/anaphylaxis in IgA deficiency</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Monitor those at risk of acute renal function</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Hyperproteinaemia, change in serum viscosity and electrolyte imbalances</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>Thrombosis</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>Aseptic meningitis syndrome</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>Hemolytic anemia</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Pulmonary adverse reactions (TRALI)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Volume overload</td>
<td>✔</td>
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</tr>
<tr>
<td>Contain infectious agents (e.g., viruses)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Do not administer SC</td>
<td>✔</td>
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<tr>
<td>Passive transfer of antibodies confounds serologic testing</td>
<td>✔</td>
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</table>

- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 5% liquid with some glucometer and test strip systems
- Patients receiving Flebogamma-DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for development of fever, chill, nausea and vomiting.

Table 7. Clinical Pharmacology

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Cmax</th>
<th>Mean AUC</th>
<th>Mean Half-life</th>
<th>Trough IgG level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammaked A</td>
<td>19 ± 3.1 mg/mL Not reported</td>
<td>7640 mg<em>hr/mL 1947 mg</em>h/mL</td>
<td>35.7 days</td>
<td>9.6 mg/mL 11.4 mg/mL</td>
</tr>
<tr>
<td>Gamunex-C IV C</td>
<td>19 ± 3.1 mg/mL Not reported</td>
<td>7640 mg<em>hr/mL 1947 mg</em>h/mL</td>
<td>35.7 days</td>
<td>9.6 mg/mL 11.4 mg/mL</td>
</tr>
<tr>
<td>Gamunex-C SC</td>
<td>16.7 ± 3.2 mg/mL</td>
<td>7022 ± 1179 mg*hr/mL</td>
<td>40.7 ± 17 days</td>
<td>Q3W: 881.6 ± 151.5 mg/dL Q4W: 763.5 ± 156.8 mg/dL</td>
</tr>
</tbody>
</table>

Author: B. Fouts, Pharm.D.
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2184 ± 293 mg/dL</td>
<td>2122 ± 425 mg/dL</td>
<td>1060 mg/dL</td>
<td>1190 mg/dL</td>
<td>2050 mg/dL</td>
<td>1939 mg/dL</td>
<td>2050 mg/dL</td>
<td>Not studied</td>
<td>2550 ± 400 mg/dl</td>
<td>2260 ± 530 mg/dl</td>
<td>Not studied</td>
<td>195 ± 28.3 mg/mL</td>
</tr>
<tr>
<td></td>
<td>27841 ± 4925 day*mg/dL</td>
<td>35509 ± 6472 day*mg/dL</td>
<td>6292 days*mg/dL</td>
<td>8792 day*mg/dL</td>
<td>29139 days*mg/dL</td>
<td>9176 days*mg/dL</td>
<td>32820 ± 6260 day*mg/dL</td>
<td>36390 ± 5950 day*mg/dL</td>
<td>3395 ± 452.7 day*mg/dL</td>
<td>3423.7 ± 397.2 day*mg/dL</td>
<td>Not studied</td>
<td>209.2 ± 36.6 mg/dL</td>
</tr>
<tr>
<td></td>
<td>19.6 ± 4.1 days</td>
<td>33.5 ± 10.7 days</td>
<td>6.3 days</td>
<td>6 days</td>
<td>35 days</td>
<td>Not reported</td>
<td>27.6 ± 5.9 days</td>
<td>45.4 ± 18.5 days</td>
<td>34 ± 10 days</td>
<td>37 ± 13 days</td>
<td>97.6 ± 16.5 mg/mL</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>996 ± 17.6 mg/dL</td>
<td>1106 ± 396 mg/dL</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not reported</td>
<td>Not studied</td>
<td>1230 ± 230 mg/dL</td>
<td>1000 ± 200 mg/dL</td>
<td>Not studied</td>
<td>87.7 ± 12.6 mg/mL</td>
</tr>
<tr>
<td></td>
<td>2182 ± 4925 day*mg/dL</td>
<td>35509 ± 6472 day*mg/dL</td>
<td>6292 days*mg/dL</td>
<td>8792 day*mg/dL</td>
<td>29139 days*mg/dL</td>
<td>9176 days*mg/dL</td>
<td>32820 ± 6260 day*mg/dL</td>
<td>36390 ± 5950 day*mg/dL</td>
<td>3395 ± 452.7 day*mg/dL</td>
<td>3423.7 ± 397.2 day*mg/dL</td>
<td>Not studied</td>
<td>209.2 ± 36.6 mg/dL</td>
</tr>
<tr>
<td></td>
<td>19.6 ± 4.1 days</td>
<td>33.5 ± 10.7 days</td>
<td>6.3 days</td>
<td>6 days</td>
<td>35 days</td>
<td>Not reported</td>
<td>27.6 ± 5.9 days</td>
<td>45.4 ± 18.5 days</td>
<td>34 ± 10 days</td>
<td>37 ± 13 days</td>
<td>97.6 ± 16.5 mg/mL</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>996 ± 17.6 mg/dL</td>
<td>1106 ± 396 mg/dL</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not reported</td>
<td>Not studied</td>
<td>1230 ± 230 mg/dL</td>
<td>1000 ± 200 mg/dL</td>
<td>Not studied</td>
<td>87.7 ± 12.6 mg/mL</td>
</tr>
<tr>
<td></td>
<td>2182 ± 4925 day*mg/dL</td>
<td>35509 ± 6472 day*mg/dL</td>
<td>6292 days*mg/dL</td>
<td>8792 day*mg/dL</td>
<td>29139 days*mg/dL</td>
<td>9176 days*mg/dL</td>
<td>32820 ± 6260 day*mg/dL</td>
<td>36390 ± 5950 day*mg/dL</td>
<td>3395 ± 452.7 day*mg/dL</td>
<td>3423.7 ± 397.2 day*mg/dL</td>
<td>Not studied</td>
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<td></td>
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<td>6.3 days</td>
<td>6 days</td>
<td>35 days</td>
<td>Not reported</td>
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<td>45.4 ± 18.5 days</td>
<td>34 ± 10 days</td>
<td>37 ± 13 days</td>
<td>97.6 ± 16.5 mg/mL</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>996 ± 17.6 mg/dL</td>
<td>1106 ± 396 mg/dL</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not reported</td>
<td>Not studied</td>
<td>1230 ± 230 mg/dL</td>
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<td>Not studied</td>
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</tr>
<tr>
<td></td>
<td>2182 ± 4925 day*mg/dL</td>
<td>35509 ± 6472 day*mg/dL</td>
<td>6292 days*mg/dL</td>
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<td>29139 days*mg/dL</td>
<td>9176 days*mg/dL</td>
<td>32820 ± 6260 day*mg/dL</td>
<td>36390 ± 5950 day*mg/dL</td>
<td>3395 ± 452.7 day*mg/dL</td>
<td>3423.7 ± 397.2 day*mg/dL</td>
<td>Not studied</td>
<td>209.2 ± 36.6 mg/dL</td>
</tr>
<tr>
<td></td>
<td>19.6 ± 4.1 days</td>
<td>33.5 ± 10.7 days</td>
<td>6.3 days</td>
<td>6 days</td>
<td>35 days</td>
<td>Not reported</td>
<td>27.6 ± 5.9 days</td>
<td>45.4 ± 18.5 days</td>
<td>34 ± 10 days</td>
<td>37 ± 13 days</td>
<td>97.6 ± 16.5 mg/mL</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>996 ± 17.6 mg/dL</td>
<td>1106 ± 396 mg/dL</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not studied</td>
<td>Not reported</td>
<td>Not studied</td>
<td>1230 ± 230 mg/dL</td>
<td>1000 ± 200 mg/dL</td>
<td>Not studied</td>
<td>87.7 ± 12.6 mg/mL</td>
</tr>
</tbody>
</table>

Author: B. Fouts, Pharm.D.
DRUG USE EVALUATION: OFF-LABEL USE OF IMMUNE GLOBULIN G

The Immunoglobulin G (IgG) drug class evidence review on products identified strong evidence to support the use of intravenous and subcutaneous IgG for primary immunodeficiency and little evidence preferring one route over the other. The goal of this evaluation is to define the appropriate off-label uses for IgG products and to assess Oregon Health Plan fee-for-service (OHP FFS) patients for appropriate use based on diagnosis and dosing with the available data.

Background:
Replacement IgG is approved by the US Food and Drug Administration (FDA) for treatment of primary humoral immunodeficiency (i.e. common variable immunodeficiency), multifocal motor neuropathy, beta-cell chronic lymphocytic leukemia, immune thrombocytopenic purpura, Kawasaki syndrome, and chronic inflammatory demyelinating polyneuropathy. Primary immunodeficiency diseases are a group of greater than 150 genetically determined conditions including those which are caused by defects in antibody production, cellular or combined defects, phagocytic cell immune defects, and complement defects; all of which may result in recurrent or unusual infections. There are also many off-label indications with evidence and guidelines supporting the use of IgG.

Good quality, evidence-based Australian (2012) and British (2008) guidelines are published and generally similar in recommendations. The Australian guidelines (Appendix 1) determine whether a condition has an established therapeutic role or an emerging therapeutic role for IgG, whether IgG should be used in exceptional circumstances only or whether IgG use is not supported. Australian guidelines recommend additional qualifying criteria for IgG treatment for inflammatory myopathies, for hypogammaglobulinemia secondary to hematopoietic stem cell transplant and for complications of renal transplantation. Despite there being only small case studies to support IgG use in prevention or treatment of fetal or neonatal thrombocytopenia or hemorrhage, the Australian guidelines recommend use with qualifying criteria. The British guidelines (Appendix 2) categorize IgG appropriateness as: yes (appropriate in all cases), selected (appropriate in selected cases with treatment priority defined as high, moderate, or low) and no (not appropriate). The guidelines agree that amyotrophic lateral sclerosis, asthma, autism, recurrent spontaneous pregnancy loss, rheumatoid arthritis, and sepsis are conditions for which treatment with IgG is not supported or appropriate. Each guideline also exclusively lists various other conditions in this category.

A 2005 position statement on the appropriate use of IgG by the American Academy of Allergy Asthma & Immunology (AAAAI) recommends treatment in the following non-FDA approved conditions: Guillain-Barré syndrome, solid organ transplant recipients who experience acute rejection or who are HLA-sensitized for acute rejection, and toxic epidermal necrolysis/Stevens-Johnson syndrome. The statement also mentioned conditions for which they could not make a recommendation, did not recommend, or conditions for which there is some data supporting IgG treatment. The criteria are summarized in Appendix 3.
Table 1 summarizes the agreement among these four sources. All FDA approved indications, Australian “established role” indications and British “yes” indications are included. AAAAI, Australian “emerging” and British “selected-high priority” indications were included if it was in agreement with the aforementioned group. There is a large grey area where the evidence supporting use of IgG in selected conditions is interpreted differently. Therefore, a case by case assessment of appropriateness may need to be done.

The recommended dose for each indication varies considerably (Table 1). Idaho Medicaid reported at a recent Drug Effectiveness Review Project meeting they realized a 25% cost avoidance from a single patient’s therapy by correcting the dose for an obese patient to the recommended adjusted body weight rather than the actual body weight. Adjusted body weight is recommended by the British guidelines based upon two small studies. Additionally, their review found a billing error where an office billed for immune globulin (brand name Privigen) 500mg as a single dose for four separate patients. The patients had actually received promethazine 50mg injectable.

Methods:
Patients with paid fee-for-service drug or professional claims for IgG from January 1, 2013 to December 31, 2013 were identified using the identifiers in Appendix 4. A claims summary of drug and professional claims for the last 13 months was reviewed for potential IgG indications. There were no minimum eligibility requirements or exclusions applied. Each patient was exclusively categorized in priority as: FDA approved diagnosis, evidence-supported off-label use, or unsupported off-label use.

In a subset of Oregon Health & Science University (OHSU) patients, the diagnosis, prescribed dose and weight was collected from the patient chart. This information was used to verify and supplement the claims diagnostic information and to verify dosing.
TABLE 1. SUMMARY OF RECOMMENDED IGG INDICATIONS FROM FDA, AUSTRALIA, BRITAIN, AND AAAAI

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dose from MicroMedex or AHFS</th>
<th>FDA</th>
<th>AAAAI</th>
<th>Australian &quot;Established Role&quot;</th>
<th>Australian &quot;Emerging Role&quot;</th>
<th>British &quot;Yes&quot;</th>
<th>British &quot;Selected - HIGH&quot;</th>
<th>Agreement Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary humoral immunodeficiency (i.e. common variable immunodeficiency)</td>
<td>200 - 800 mg/kg IV infusion once every 3 to 4 week</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>immune thrombocytopenic purpura (ITP)</td>
<td>400 – 1000mg/kg IV QD x 2-5 days</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>2000mg/kg x1 or 400mg/kg QD x 4 days</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>chronic inflammatory demyelinating polyneuropathy</td>
<td>1000mg/kg every 3 weeks</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Acquired hypogammaglobulinemia secondary to hematological malignancies</td>
<td>400mg/kg every 3-4 weeks.</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>(including beta-cell chronic lymphocytic leukemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multifocal motor neuropathy</td>
<td>500-2500mg/kg every 4 weeks</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>400mg/kg QD x 5 days</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>toxic epidermal necrolysis/Stevens-Johnson syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>solid organ transplantation</td>
<td>IVIg with plasma exchange: 0.1 to 0.5 g/kg IVIg alone: 2 g/kg to a maximum of 140 g as a single dose, or 2 to 3.5 g/kg in a divided dose.*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>inflammatory myopathies (dermatomyositis, polymyositis, inclusion body myositis)</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>feto-maternal/neonatal alloimmune thrombocytopenia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>IgM paraproteinemic neuropathy</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>myasthenia gravis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neonatal hemochromatosis</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>stiff person syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumonitis induced by cytomegalovirus following transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A "1" indicates the organization listed the diagnosis. These were summed across the row to determine agreement. A "4" indicates total agreement with FDA, AAAAI, Australia and British guidelines. *Dose for kidney transplant rejection provided by Australian guidelines.
Results:
There were 33 IgG patients identified. The majority of patients were female (67%) and over the age of 18 (85%). Eight patients were being managed by OHSU. Table 2 summarizes the patient demographics. During 2013, OHP FFS reimbursed $328,872 for IgG for these patients. Table 3 summarizes the distribution of products used.

Without scrutiny of the specific approved indications for each individual product, 24 (73%) patients had an FDA-approved diagnosis. A summary of these results, using the most applicable diagnosis of record for each individual, are in Table 3.

### TABLE 2: PATIENT DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Demographic</th>
<th>n = 33</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>22</td>
<td>67%</td>
</tr>
<tr>
<td>≤18 years old</td>
<td>5</td>
<td>15%</td>
</tr>
<tr>
<td>Mean Age (range)</td>
<td>41 (2-77)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Managing Facility Distribution**

<table>
<thead>
<tr>
<th>Managing Facility</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHSU</td>
<td>8</td>
<td>24%</td>
</tr>
<tr>
<td>Providence</td>
<td>6</td>
<td>18%</td>
</tr>
<tr>
<td>PeaceHealth</td>
<td>5</td>
<td>15%</td>
</tr>
<tr>
<td>Legacy Good Samaritan</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Mid Valley Healthcare</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Hematology Oncology of Salem</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Legacy Emanuel</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>St. Charles</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Allergy and Asthma Center</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Saint Alphonsus</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Asante Three Rivers</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Grande Ronde</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Albany General</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Northwest Cancer Specialists</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>
### TABLE 3. IgG PRODUCT UTILIZATION SUMMARY

<table>
<thead>
<tr>
<th>Code</th>
<th>Descriptions</th>
<th>Patient Count</th>
<th>Claim Count</th>
<th>Paid Amount</th>
<th>Other Ins</th>
<th>Market Share by Paid Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
<td>9</td>
<td>53</td>
<td>$123,633</td>
<td>$0</td>
<td>38%</td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
<td>12</td>
<td>43</td>
<td>$80,447</td>
<td>$0</td>
<td>24%</td>
</tr>
<tr>
<td>NDC</td>
<td>HiZENTRA</td>
<td>2</td>
<td>20</td>
<td>$69,311</td>
<td>$15,426</td>
<td>21%</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg</td>
<td>8</td>
<td>22</td>
<td>$30,907</td>
<td>$0</td>
<td>9%</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)</td>
<td>1</td>
<td>3</td>
<td>$9,598</td>
<td>$0</td>
<td>3%</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
<td>3</td>
<td>9</td>
<td>$6,541</td>
<td>$0</td>
<td>2%</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
<td>2</td>
<td>12</td>
<td>$5,963</td>
<td>$0</td>
<td>2%</td>
</tr>
<tr>
<td>NDC</td>
<td>GAMMAGARD LIQUID</td>
<td>1</td>
<td>2</td>
<td>$1,814</td>
<td>$6,585</td>
<td>1%</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
<td>1</td>
<td>2</td>
<td>$656</td>
<td>$0</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Unique Totals:**
- 33
- 166
- $328,872
- $22,012

Table 3: Diagnoses for patient claims.

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>n=33</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approved diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27906 Common Variable Immunodeficiency</td>
<td>9</td>
<td>27%</td>
</tr>
<tr>
<td>28731 Immune Thrombocytopenic Purpura</td>
<td>5</td>
<td>15%</td>
</tr>
<tr>
<td>35781 Chronic inflammatory demyelinating polyneuritis</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>27903 Other selective immunoglobulin deficiencies</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>27900 Hypogammaglobulinemia</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>4461 Acute febrile mucocutaneous lymph node syndrome (Kawasaki Disease)</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Evidence-supported off-label diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7103 Dermatomyositis</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>7104 Polymyositis</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>99681 Complications of transplanted kidney</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>99688 Complications of transplanted organ, stem cell</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>67803 Fetal hematologic conditions, antepartum condition or complication</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Other off-label diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7100 Systemic lupus erythematosus</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>

March 3, 2014
Author: J.Lee/Ketchum
Table 4 is a summary of the verification and dose of the OHSU patients. Seven of the patients used Gammagard Liquid and one used Gamunex-C / Gammaked. Two patients are potentially not being dosed as recommended. Patient #5 has only received a single dose and the recommended dose is every 3-4 weeks. Patient #7 may need to be dosed with adjusted body weight.

**TABLE 4 – SUMMARY OF OHSU ANALYSIS**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Diagnosis</th>
<th>Weight (kg)</th>
<th>Height (in)</th>
<th>IBW (kg)</th>
<th>ABW (kg)</th>
<th>Prescribed Dose</th>
<th>Prescribed Freq</th>
<th>Calc max dose (g)</th>
<th>Appropriate dose?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic inflammatory neuropathy, sarcoidosis</td>
<td>64.4</td>
<td>64.0</td>
<td>54.7</td>
<td>N/A</td>
<td>65 g (1 g/kg)</td>
<td>q3weeks</td>
<td>64</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>Common Variable Immunodeficiency</td>
<td>73.2</td>
<td>68.5</td>
<td>69.6</td>
<td>N/A</td>
<td>25g (0.3/kg)</td>
<td>q2weeks</td>
<td>44</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>Common Variable Immunodeficiency</td>
<td>49.9</td>
<td>61.0</td>
<td>52.4</td>
<td>N/A</td>
<td>40 g (0.8g/kg)</td>
<td>q4weeks?</td>
<td>40</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>hypogammaglobulinemia, immunocompromised, graft vs. host disease (bone marrow)</td>
<td>59.6</td>
<td>73.0</td>
<td>79.9</td>
<td>N/A</td>
<td>10-30 g (0.2-0.5g/kg)</td>
<td>q4weeks</td>
<td>24</td>
<td>Y (deceased)</td>
</tr>
<tr>
<td>5</td>
<td>Common Variable Immunodeficiency</td>
<td>64.0</td>
<td>61.5</td>
<td>49.0</td>
<td>N/A</td>
<td>15 g (0.3 g/kg)</td>
<td>Once</td>
<td>38</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>28731 Immune Thrombocytopenic Purpura</td>
<td>14.7</td>
<td>33.6</td>
<td>N/A</td>
<td>N/A</td>
<td>15 g (1 g/kg)</td>
<td>Once</td>
<td>15</td>
<td>Y (ITP resolved)</td>
</tr>
<tr>
<td>7</td>
<td>Kidney transplant rejection</td>
<td>75.1</td>
<td>56.3</td>
<td>41.5</td>
<td>54.9</td>
<td>140 g (2 g/kg)</td>
<td>Once</td>
<td>110</td>
<td>N (Too high?)</td>
</tr>
<tr>
<td>8</td>
<td>Kidney transplant rejection</td>
<td>67.2</td>
<td>68.0</td>
<td>63.9</td>
<td>N/A</td>
<td>30 g (0.5 g/kg)</td>
<td>Once</td>
<td>34</td>
<td>Y</td>
</tr>
</tbody>
</table>
Discussion:
Using a consensus of the FDA indications and AAAAI, Australian and British guidelines to indicate evidence supporting the use of IgG, 24 (73%) patients had a documented FDA-approved indication. Another 8 (24%) patients had documentation of an evidence supported indication. The claims analysis found 2 patients had diagnoses that needed further evaluation: Systemic lupus erythematosus and sarcoidosis.

Recommendations on thrombocytopenia secondary to sarcoidosis were not made in any of the guidelines.\textsuperscript{5,6,7} Upon review, this particular patient’s chart at OHSU indicated the patient also had chronic inflammatory neuropathy. The dosing schedule was consistent with a diagnosis of chronic inflammatory demyelinating polyneuropathy, an FDA-approved condition. The patient was re-categorized.

Thus, a single patient may have been prescribed IgG for a diagnosis with little evidence of benefit. Only a very small open-label trial consisting of 12 patients and scanty case reports are available to support the use of IgG in patients with systemic lupus erythematosus (SLE).\textsuperscript{9} The Australian guidelines do not support use of IgG in patients with SLE due to preferable treatments being available.\textsuperscript{5} It is possible this patient may have a qualifying diagnosis that was not included on claims to OHP FFS.

Two (25%) of the 8 OHSU patients were potentially dosed inappropriately. One patient with primary immunodeficiency received only 1 dose, whereas recommendations are to receive treatment every 3 to 4 weeks. It is possible this patient lost OHP FFS eligibility or died. Another apparently obese patient appeared to be dosed using the actual body weight rather than the adjusted body weight. This resulted an approximate 20% excessive dose (140 grams versus 110 grams).

There was some evidence of inappropriate use of IgG in OHP FFS in 2013. Given the high cost of IgG, any inappropriate use can be very costly. The mean cost per patient-year in 2013 was almost $10,000. However, development, maintenance and application of accurate drug use criteria in this rapidly changing and diverse field would be onerous.

Recommendations:

1) Perform a retrospective quarterly audit and report to P&T for all IgG claims to verify billing accuracy, evidence supported diagnosis and appropriate dosing.
References:


### Appendix: Australian criteria for the clinical use of immunoglobulin

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditions for which IgG has an established therapeutic role</strong></td>
<td>Acquired hypogammaglobulinemia secondary to hematological malignancies, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults, inflammatory myopathies (dermatomyositis, polymyositis, inclusion body myositis), Kawasaki disease, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, myasthenia gravis, neonatal hemochromatosis, primary immunodeficiency diseases, stiff person syndrome</td>
</tr>
<tr>
<td><strong>Conditions for which IgG has an emerging therapeutic role</strong></td>
<td>Acute disseminated encephalomyelitis, ANCA-positive systemic necrotizing vasculitis, autoimmune hemolytic anemia, bullous pemphigoid, cicatricial pemphigoid, Evans syndrome-autoimmune hemolytic anemia with immune thrombocytopenia, feto-maternal/neonatal alloimmune thrombocytopenia, hemophagocytic syndrome, idiopathic (autoimmune) thrombocytopenia purpura (ITP) in children, IgM paraproteinemic neuropathy, kidney transplantation, multiple sclerosis, opsoclonus myoclonus ataxia, pemphigus foliaceus, pemphigus vulgaris, post-transfusion purpura, secondary hypogammaglobulinemia (including iatrogenic immunodeficiency), specific antibody deficiency (including IgG subclasses), toxic epidermal necrolysis/Stevens-Johnson syndrome, toxic shock syndrome</td>
</tr>
<tr>
<td><strong>Conditions for which IgG use is supported in exceptional circumstances only</strong></td>
<td>Acute leukemia in children, autoimmune congenital heart block, autoimmune neutropenia, autoimmune uveitis, catastrophic antiphospholipid syndrome, coagulation factor inhibitors, Devic disease, diabetic amyotrophy, epidermolysis bullosa acquisita, epilepsy, Graves ophthalmopathy, hemolytic disease of the newborn, hemolytic transfusion reaction, Hashimoto encephalopathy, HIV in children, limbic encephalitis (nonparaneoplastic), myocarditis in children, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, paraneoplastic syndromes (subacute sensory neuropathy, cerebellar degeneration, limbic encephalitis), potassium channel antibody-associated encephalopathy, pure red cell aplasia, pure white cell aplasia, pyoderma gangrenosum, Rasmussen syndrome, scleromyxedema, Sjogren’s syndrome, solid organ transplantation (other than kidney), Susac syndrome, systemic capillary leak syndrome</td>
</tr>
<tr>
<td><strong>Conditions for which IgG use is not supported</strong></td>
<td>Acute optic neuritis, acute rheumatic fever, adrenoleukodystrophy, amegakaryocytic thrombocytopenia, antiphospholipid syndrome (non-obstetric), aplastic anemia/pancytopenia, asthma, atopic dermatitis/eczema-adult, autism, autologous hemopoietic stem cell transplantation, Hehçet’s disease, cardiac surgery with bypass-prophylaxis, congestive cardiac failure, Crohn’s disease, Diamond Blackfan syndrome, female infertility, glomerulonephritis-IgA nephritis, hemolytic uremic syndrome, Henoch-Schonlein purpura, HIV/AIDS-adult, idiopathic dilated cardiomyopathy, linear IgA disease, lupus cerebritis, lupus nephritis, motor neuron disease/amyotrophic lateral sclerosis, myalgic encephalomyelitis, narcolepsy/cataplexy, nephrotic syndrome, obsessive compulsive disorders, polynephropathy of critical illness, recurrent fetal loss (with or without antiphospholipid syndrome), rheumatoid arthritis, sepsis, sickle cell disease, systemic lupus erythematosus, ulcerative colitis</td>
</tr>
</tbody>
</table>
## Appendix 2: British criteria for the clinical use of immunoglobulin

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate in all cases if the physician wants to prescribe it</td>
<td>Kawasaki disease, primary immunodeficiencies, alloimmune thrombocytopenia-fetal therapy (treatment to the mother), low serum IgG levels after hematopoietic stem cell transplant for malignancy, toxic epidermal necrolysis/Stevens-Johnson syndrome, pneumonitis induced by cytomegalovirus following transplantation</td>
</tr>
<tr>
<td>Appropriate in only selected cases and in these, only if the physician wants to prescribe it (high priority)</td>
<td>Alloimmune thrombocytopenia-neonatal therapy, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura-pediatric (&lt;16 years), idiopathic thrombocytopenic purpura-adult, chronic inflammatory demyelinating polyradiculois neuropathy, Guillain-Barré syndrome, paraprotein associated demyelinating neuropathy (IgG or IgA), alloimmune thrombocytopenia-neonatal therapy, idiopathic thrombocytopenic purpura-pediatric (&lt;16 years), juvenile dermatomyositis, dermatomyositis</td>
</tr>
<tr>
<td>Appropriate in only selected cases and in these, only if the physician wants to prescribe it (moderate priority)</td>
<td>Impaired specific antibody production, acquired red cell aplasia caused by parvovirus B19, adult HIV associated thrombocytopenia, autoimmune (acquired) hemophilia, autoimmune hemolytic anemia, Avans’ syndrome, hemolytic disease of the fetus and newborn (isoimmune hemolytic jaundice in neonates), hemophagocytic lymphohistiocytosis/hemophagocytic syndrome, post-transfusion purpura, chronic lymphocytic leukemia, multiple myeloma, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, myasthenia gravis, paraprotein associated demyelinating neuropathy (IgM), Rasmussen syndrome, stiff person syndrome, immunobullous diseases, fetal hydrops, hemolytic disease of the fetus and newborn (isoimmune hemolytic jaundice in neonates), toxin related infection in pediatric intensive care, necrotizing (associated with Panton Valentine leukocidin) staphylococcal sepsis, severe invasive group A streptococcal disease, severe or recurrent <em>Clostridium difficile</em> colitis, staphylococcal toxic shock syndrome</td>
</tr>
<tr>
<td>Low treatment priority due to weak evidence base</td>
<td>Secondary antibody deficiencies, acquired red cell aplasia not caused by parvovirus B19, acquired von Willebrand’s disease, aplastic anemia or pancytopenia, autoimmune neutropenia, hemolytic uremic syndrome, post-exposure prophylaxis for viral infection if intramuscular injection is contraindicated or if hyperimmune immunoglobulins are not available, post-transfusion hyperhemolysis (usually in patients with sickle cell disease), graft versus host disease after allogeneic bone marrow transplant or hematopoietic stem cell transplant, infection after allogeneic bone marrow transplant or hematopoietic stem cell transplant, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS), acute disseminated encephalomyelitis, acute idiopathic dysautonomia, autoimmune diabetic proximal neuropathy, Bickerstaff’s brain stem encephalitis, central nervous system vasculitis, cerebral infarction with antiphospholipid antibodies, intractable childhood epilepsy, neuromyotonia, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), polymyositis polyneuropathy organomegaly endocrinopathy, monoclonal gammopathy skin changes (POEMS), potassium channel antibody associated non-neoplastic limbic encephalitis, vasculitic neuropathy, atopic dermatitis or eczema, pyoderma gangrenosum, urticarial, intractable childhood epilepsy, juvenile systemic lupus erythematosus, other systemic vasculitides, systemic juvenile idiopathic arthritis, catastrophic antiphospholipid syndrome, polymyositis, systemic lupus erythematosus, systemic lupus erythematosus with secondary immunocytopenia, systemic vasculitides and antineutrophil cytoplasmic antibody disorders, acute antibody mediated rejection after solid organ transplantation</td>
</tr>
<tr>
<td>Not appropriate</td>
<td>Immunodeficiency secondary to pediatric HIV infection, autologous bone marrow transplant, adrenoleukodystrophy, Alzheimer’s disease, amyotrophic lateral sclerosis, autism, chronic fatigue syndrome, critical illness neuropathy, inclusion body myositis, multiple sclerosis, rheumatoid arthritis, neonatal sepsis (prevention or treatment), sepsis in the intensive care unit not related to specific toxins or <em>Clostridium difficile</em>, asthma, autoimmune uveitis, Graves’ ophthalmopathy, failure of in vitro fertilization, recurrent spontaneous pregnancy loss</td>
</tr>
</tbody>
</table>
### Appendix 3: AAAAI Recommendations for the Appropriate use of IgG

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>FDA approved: Primary immunodeficiencies; prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia; prevention of coronary artery aneurysm in Kawasaki disease; prevention of infections and graft versus host disease after bone marrow transplantation; reduction of serious bacterial infection in HIV-infected children; increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding</td>
</tr>
<tr>
<td></td>
<td>Non-approved: post-transfusion purpura; Guillain-Barré syndrome; chronic inflammatory demyelinating polyneuropathy; multifocal motor neuropathy; solid organ transplant recipients who experience acute rejection or who are HLA-sensitized for acute rejection; toxic epidermal necrolysis/Stevens-Johnson syndrome</td>
</tr>
<tr>
<td><strong>Statement of evidence of some benefit</strong></td>
<td>B cell chronic lymphocytic leukemia; HIV infected children; autoimmune thrombocytopenia; autoimmune hemolytic anemia; Evans syndrome; acquired hemophilia; rheumatoid arthritis; antiphospholipid antibody syndrome-related recurrent spontaneous abortion, in vitro fertilization; anti-neutrophil cytoplasmic antibody disorders; systemic sclerosis/scleroderma; Still’s disease; individuals with antibody deficiency who have asthma-like symptoms; myasthenia gravis; Lambert Eaton myasthenic syndrome; relapsing-remitting multiple sclerosis; patients undergoing allogenic transplantation; autoimmune cytophenias occurring post-transplant; established bacterial septic shock; group B streptococcal disease; meningoencephalitis caused by enteroviral infection, pneumonitis caused by CMV; RSV pneumonitis in immunodeficient patients; cystic fibrosis</td>
</tr>
<tr>
<td><strong>Recommended only with reservations</strong></td>
<td>Organ-related complications of systemic lupus erythematosus including nephritis, myocarditis, polyradiculopathy, and bone marrow suppression; Graves’ ophthalmopathy; autoimmune uveitis; autoimmune chronic active hepatitis; intractable childhood epilepsy syndromes; bullous pemphigoid or other autoimmune blistering disorders</td>
</tr>
<tr>
<td><strong>Not recommended or unable to make recommendation</strong></td>
<td>Sepsis beyond neonatal period; multiple trauma; post-operative wounds; inflammatory myopathies; polymyositis; dermatomyositis; inclusion body myositis; severe asthma; acute graft versus host disease; anemia caused by chronic erythroivirus B-19 infection; <em>Campylobacter jejuni</em>; pseudomembranous colitis caused by <em>Clostridium difficile</em>; suspected sepsis; CMV gastroenteritis; established bacterial pneumonia; urticarial; atopic dermatitis; psoriasis; autism; chronic fatigue syndrome; pediatric autoimmune neuropsychiatric disorders with associated streptococcal infection (PANDAS); acute myocarditis; carditis of acute rheumatic fever; recently diagnosed dilated cardiomyopathy; pregnancy in women who experience recurrent spontaneous abortion</td>
</tr>
</tbody>
</table>
# Appendix 4 – Drug Identifiers

<table>
<thead>
<tr>
<th>ProcCode</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>90283</td>
<td>Immune Globulin (IgIV), human, for intravenous use</td>
</tr>
<tr>
<td>90284</td>
<td>Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each</td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1556</td>
<td>Injection, immune globulin (Bivigam), 500 mg</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HSN</th>
<th>Generic Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>025631</td>
<td>IMMUNE GLOB,GAM CAPRYLATE(IGG)</td>
</tr>
<tr>
<td>033220</td>
<td>IMMUNE GLOBULIN,G(IGG)/MALTOSE</td>
</tr>
<tr>
<td>004202</td>
<td>IMMUNE GLOBULIN,GAMMA(IGG)</td>
</tr>
</tbody>
</table>
Abbreviated Class Update: Hepatitis C

Month/Year of Review: March 2014
Current PDL Class: Hepatitis C Agents

Last Review: September 2013
Source Document: OSU College of Pharmacy

Preferred Agents: BOCEPREVIR (VICTRELIS®), TELAPREVIR (INCIVEK®), SOFOSBUVIR (SOLVALDI®), SIMEPREVIR (OLYSIO®), PEGINTERFERON ALPHA-2A (PEGASYS®), PEGINTERFERON ALPHA-2A SUBQ (PEGASYS®, PEGASYS PROCLICK®), PEGINTERFERON ALFA-2B, PEGINTERFERON ALFA-2B, RIBAVIRIN

Non-Preferred Agents: INTERFERON ALFACON-1 (INGERGEN®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

Current PA: Prior authorizations are currently in place or have been recommended for pegylated interferon and ribavirin (PR), for the oral protease inhibitors, and for sofosbuvir (Appendix 1) to ensure treatments are supported by the medical literature.

Research Questions:
• Is there any new evidence about comparative effectiveness of antiviral regimens, in long term clinical outcomes such as mortality and hepatitis C complications or in sustained virologic response (SVR) in adult patients being treated for chronic Hepatitis C virus (HCV)?
• Is there any new evidence about comparative harms of antiviral regimens in adult patients being treated for chronic HCV?
• Are there subpopulations of patients with HCV for which one antiviral regimen is more effective or associated with less harm?

Conclusions:
• In Genotype 1 treatment naïve patients and treatment experienced patients, there is insufficient to low quality evidence that simeprevir does not appear to significantly improve the SVR12 compared with triple therapy with boceprevir and telaprevir, and its effectiveness is diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. 1 Simeprevir requires peginterferon and ribavirin (PR) and cannot be used to treat interferon-ineligible patients. There is an ongoing randomized trial comparing simeprevir to telaprevir is the first trial directly comparing 2 antiviral agents. Sofosbuvir therapy appears to have the highest SVR12 in this population (83%; 95% CI 79% to 87%). 1
• There is insufficient evidence to evaluate the use of simeprevir or sofosbuvir in treatment-naïve genotype 1 patients who are interferon-ineligible.
• There is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients or simeprevir plus PR.
• There is moderate quality evidence that in genotypes 2 and 3 CHC, sofosbuvir-based therapy improves SVR rates compared to dual therapy with pegylated interferon and ribavirin.
• There is low quality evidence, based on one unpublished open-label trial, that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks results in high SVR12 rates (79-96%) in HCV genotype 1 null responders with METAVIR F0-F2 fibrosis. 2
There is insufficient evidence that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks is efficacious in HCV genotype 2 treatment naïve and null responder patients with METAVIR F3-F4 fibrosis. Only preliminary data is available demonstrating SVR4 rates of 96-100%; SVR12 rates have not yet been released.2

There is insufficient evidence evaluating the safety and efficacy of simeprevir in HCV patients with moderate or severe hepatic impairment. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 ULN or lower, and transaminase level of 10 x ULN or lower. It should be limited to patients with compensated liver disease.

There is insufficient data evaluating sofosbuvir in patients with severe renal impairment (CrCl <30 ml/min) or those who require hemodialysis. There is no dosing data currently available for this patient population.

Recommendations:
- Recommend revising sofosbuvir prior authorization criteria for appropriate patient selection, including criteria to avoid in patients with significant renal impairment, those with decompensated liver disease, and those who would not be noncompliant for a variety of reasons (Appendix 1).
- Continue to evaluate new evidence as it comes out for further revisions.
- Evaluate comparative costs in executive session for PDL decisions.

Previous Conclusions and Recommendations:

Class Update
- There is moderate strength evidence from a recent AHRQ report of a lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b plus ribavirin compared to dual therapy with pegylated interferon alfa-2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I²=27.4%), with an absolute difference in SVR rates of 8 percentage points, while dual therapy with interferon alfa-2b is associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI 0.71 to 0.88; I²=0.0%) with no differences in withdrawals due to adverse events (pooled RR 1.1, 95% CI 0.73 to 1.7, I²=42%).
- There is high quality evidence that triple therapy with either boceprevir or telaprevir produces a higher likelihood of achieving SVR as compared to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.
- There is insufficient direct comparative evidence between boceprevir (BOC) and telaprevir (TVR) on long term clinical outcomes.

Sofosbuvir
- There is poor quality evidence, based on one open-label trial, that sofosbuvir in combination with ribavirin for 12 weeks is noninferior to pegylated interferon plus ribavirin for 24 weeks in genotype 2 and 3 treatment-naïve chronic Hepatitis C (CHC) in achieving SVR at week 12 (67% for both groups).
- There is moderate quality evidence that sofosbuvir in combination with ribavirin for 12 weeks is superior to placebo in genotype 2 and 3 CHC patients who are intolerant or ineligible for interferon based therapy in achieving SVR at week 12 (78% vs. 0%; p<0.001), as well as in patients who did not have a response to interferon therapy.
- There is evidence that extending the duration of treatment in genotype 3 patients to 24 weeks improves SVR rates compared to 12 weeks of treatment. Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients.
- In genotype 1, there low quality evidence that the combination of sofosbuvir plus ribavirin plus peginterferon alfa results in higher rates of SVR at 12 weeks than historical control rates (90% vs. 60%). This is based on a single arm, open-label study.
- Based on limited data, sofosbuvir appears to have no serious adverse event concerns associated with its use and is well-tolerated for 12-16 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination...
with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. Overall discontinuations due to adverse events in trials were low (0-2%).

**Simeprevir**

- There is evidence that simeprevir in combination with peginterferon alfa and ribavirin significantly improves SVR rates compared to placebo in patients with genotype 1 CHC, in both treatment-naïve patients (80% vs. 50%) and treatment experienced (79% vs. 36%, respectively). Most of the data remains unpublished and cannot be assessed for quality.
- There is low quality evidence, based on one phase IIb trial, that simeprevir in combination with peginterferon alfa and ribavirin is effective in achieving SVR in partial and null responders.
- Compared to placebo, there is low quality evidence that simeprevir does not significantly improve SVR rates in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline. Screening patients with HCV genotype 1 for the presence of this polymorphism is strongly recommended and alternative therapy should be considered for patients infected with the Q80K polymorphism.
- There is insufficient evidence evaluating simeprevir in patients who have previously failed therapy with a treatment regimen that includes simeprevir or other HCV protease inhibitors.
- There is insufficient evidence evaluating the use of simeprevir in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The combination of simeprevir should not be used in patients with decompensated cirrhosis (moderate to severe hepatic impairment).
- There is low quality evidence of an increased risk of adverse reactions in patients of East Asian ancestry due to higher simeprevir exposure.

**Reason for Review:** New clinical practice guidelines for the treatment of chronic Hepatitis C were recently released. With the approval of the two new oral agents, these guidelines as well as any new evidence within the class will be reviewed for further decision-making.

**Background:**

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin. This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3,
the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.\(^6\)

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been initiated.\(^7\) Simeprevir structurally binds to a target enzyme which is different than telaprevir and boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.\(^4\) The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one or more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use.

**Methods:**
A Medline literature search beginning September 2013 (since the most recent Hepatitis C Class Update) and ending February 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC), telaprevir (TVR), simeprevir (SIM), and sofosbuvir (SOF) was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. The initial literature search resulted in 83 citations. After further review and exclusion of studies with drugs not yet FDA approved or already reviewed in preliminary SIM and SOF reviews, the search resulted in 7 RCTs\(^8\)\(^-\)\(^14\), 2 systematic reviews\(^1\)\(^,\)\(^15\), and 2 updated clinical practice guidelines.\(^16\)\(^,\)\(^17\)

**Systematic Reviews:**
A draft technology report from the Institute for Clinical and Economic Review (ICER) was published in February 2014.\(^1\) The assessment attempted to answer the following questions: 1) among patients with genotype 1, are treatment regimens incorporating the new DAAs equivalent or superior to the current standard of care, pegylated interferon plus ribavirin and one of the protease inhibitors; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the current standard of care, pegylated interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. There were no studies found that directly compared therapies based on simeprevir to those based on sofosbuvir or to the two protease inhibitors boceprevir and telaprevir. A network meta-analysis was done to provide indirect evidence about the relative efficacy for the drug combinations available using these therapies.
The literature search identified 327 potentially relevant studies, resulting in 21 included publications describing simeprevir or sofosbuvir. Due to the paucity of literature, unpublished trials were included as well. All of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. Results from the network meta-analysis for SVR12 among treatment naive patients infected with HCV genotype 1 are included in the following table:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12</th>
<th>95% CI</th>
<th>P versus PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>47%</td>
<td>41% to 52%</td>
<td>-</td>
</tr>
<tr>
<td>Boceprevir + PR</td>
<td>73%</td>
<td>68% to 77%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Telaprevir + PR</td>
<td>74%</td>
<td>69% to 79%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Simeprevir + PR</td>
<td>76%</td>
<td>70% to 81%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sofosbuvir + PR</td>
<td>83%</td>
<td>79% to 87%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PR: pegylated interferon + ribavirin

This suggests that simeprevir has similar SVR12 results compared to triple therapy with boceprevir or telaprevir and sofosbuvir therapy has the highest estimated SVR12. However, this is based on many assumptions as well from uncontrolled trials and therefore the evidence remains insufficient to make definitive conclusions regarding the comparative effectiveness of the agents. There were no studies for interferon-ineligible patients in treatment naive patients.

For genotype 1 treatment experienced patients, again SVR 12 for simeprevir based therapy (67%; 95% CI 59-74%) was similar as that for triple therapy with boceprevir (64%; 95% CI 40-76%) and telaprevir (70%; 95% CI 61-77%). The combination of simeprevir plus sofosbuvir had the highest estimated SVR12 (90%; 95% CI 78-96%) but this is based on extrapolations from one uncontrolled trial and therefore the uncertainty of the results remains low. There were no studies in treatment-experienced patients who were interferon-ineligible. However, the combination of simeprevir and sofosbuvir evaluated four interferon-free regimens in treatment-experienced patients. The authors concluded that there is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients and no data on sofosbuvir plus PR.

For genotype 2, the SVR24 for PR alone has shown to be 75-85%. Of the newer agents, only sofosbuvir has been approved for the treatment of genotypes 2 and 3. In genotype 2 treatment-naive patients, there were a total of 8 studies (7 in interferon-eligible and 1 in interferon-ineligible). Sofosbuvir demonstrated an improvement in SVR over the previous standard of care, treatment time is decreased from 24 to 12 weeks, and interferon is no longer needed. It has also been studied in patients unwilling, unable, or intolerant of interferon. For treatment-experienced patients none of the trials had a control group without sofosbuvir. For genotype 3 treatment-naive and treatment experienced patients, 24 weeks of sofosbuvir plus ribavirin appears to be superior to 12 or 16 weeks of the same therapy. The POSITRON data suggest that sofosbuvir plus ribavirin is effective for interferon-ineligible patients with genotype 3 and the VALENCE trial suggests that 24 weeks of therapy would be more effective than 12 weeks.

Overall, the authors noted that the addition of simeprevir to PR did not markedly increase the risk of adverse events. It was more difficult to assess the relative impact of sofosbuvir on adverse events because few of the trials randomized patients to a regimen without sofosbuvir. The most common adverse events in genotype 1 patients on sofosbuvir and PR included fatigue, headache, and flu-like illness and fewer patients stopped therapy due to adverse events than those in the PR group (2% vs. 11%). In genotype 2 and 3 patients, the elimination of interferon from the treatment regimen markedly decreased the risk for most adverse events. There were also significantly fewer grade 3 or 4 adverse events, and a reduction in discontinuation of therapy due to adverse events.
Pegylated Interferon:
A systematic search including randomized, prospective studies compared rapid virological response (RVR) and early virological response (EVR) rates of peginterferon alfa-2a vs. peginterferon alfa-2b. A total of 8 RCTs were included in the meta-analysis. The early virological response meta-analysis included 7 trials and 4359 patients and showed an overall significant increase in the percentage of patients treated with peginterferon alfa-2a that achieved EVR when compared with the peginterferon alfa-2b group (53.3% vs. 43.8%; p=0.0028). The meta-analysis of RVR included 5 trials and 3833 patients with an estimated effect in favor of peginterferon alfa-2a of 25% vs. 16.8% for peginterferon alfa-2b (p=0.0056).

Clinical Guidelines:
On January 29, 2014, the American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) / International Antiviral Society (IAS) jointly created guidelines for the treatment of chronic hepatitis C. The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, but did lack non-specialist members. Recommendations were graded in terms of the level of the evidence and strength of the recommendation, using a scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. The main recommendations are as followed:

**Treatment naïve or those who experienced relapse after prior treatment with peginterferon and ribavirin:**

**Genotype 1, interferon eligible**
1. Initial therapy with sofosbuvir plus PR for 12 weeks (Class 1, Level A recommendation).
   a. This is based on one poor quality, open-label, single-arm phase 3 NEUTRINO trial evaluating sofosbuvir in combination with pegylated interferon and ribavirin in 291 treatment-naïve patients with HCV genotype 1 infection. The SVR 12 was 89% and was lower in patients with cirrhosis.
2. Alternative regimens include daily simeprevir + PR for 12 weeks (for only those with HCV genotype 1b or HCV genotype 1a without the Q80K polymorphism). (Class IIA, Level A recommendation).
   a. The alternative regimen is based on two unpublished, randomized, placebo controlled phase 3 trials evaluating the efficacy and safety of simeprevir.
3. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).
4. Monotherapy with pegylated interferon, ribavirin, or a direct acting antiviral are not recommended (Class III, Level A recommendation).

**Genotype 1, interferon ineligible**
1. Sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks is recommended (Class I, Level B recommendation)
   a. This is based on the unpublished ongoing phase 2 COSMOS trial. This regimen should only be considered in patients who require immediate treatment.
2. Alternative regimen of sofosbuvir plus ribavirin for 24 weeks (Class IIb, Level B recommendation).
   a. This is based on one, poor quality, phase 2, open-label clinical trial in 60 treatment-naïve patients with unfavorable characteristics (African American race and advanced fibrosis).

**Genotype 2**
1. Sofosbuvir plus ribavirin for 12 weeks (Class I, Level A recommendation). There are no recommended alternative regimens.
   a. This is based on 2 fair quality and one unpublished phase 3 trials. Across all 3 trials, 94% of patients achieved SVR with sofosbuvir plus ribavirin.

**Genotype 3**
1. Sofosbuvir plus ribavirin for 24 weeks (Class I, Level B recommendation)
   a. One unpublished trial (VALENCE) demonstrated that higher response rates can be achieved with a 24-week duration of sofosbuvir than those reported for the 12 or 16 week durations studied in other trials (84% vs. 61%, respectively).

2. Alternative regimen is sofosbuvir plus ribavirin plus peginterferon alfa for 12 weeks.
   a. Two unpublished trials (PROTON and ELECTRON) have evaluated the combination of sofosbuvir + PR in patients with genotype 3 HCV and demonstrated a 97% SVR rate in treatment-naive patients. This regimen has a higher risk of adverse effects and may require increased monitoring.

Genotype 4, interferon eligible
1. Sofosbuvir + PR is recommended for 12 weeks (Class IIa, Level B recommendation). Few data is available for genotype 4 and only patients who immediate treatment is required should be treated.
   a. This is based on one poor quality, open-label, single arm study (NEUTRINO) evaluating 12 weeks of sofosbuvir. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12.

2. Alternative regimen of simeprevir for 12 weeks plus ribavirin and peginterferon for 24-48 weeks is recommended (Class IIB, level B recommendation).
   a. This is based on one ongoing phase 3 trial in patient with genotype 4.

Genotype 4, interferon ineligible
1. Sofosbuvir plus ribavirin for 24 weeks is recommended (Class IIB, Level B recommendation).
   a. This is based on a small, unpublished study of Egyptian patients in the U.S. treated with sofosbuvir plus ribavirin. SVR 12 was achieved in 11 of 14 (79%) treatment-naive patients treated for 12 weeks. SVR24 was achieved in 100% of the 14 treatment-naive patients treated for 24 weeks.

Retreatment of persons in whom prior therapy has failed (non-responders, including null responders and partial responders):
Genotype 1 nonresponders
1. Initial therapy with sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks (Class IIA, Level B recommendation).
   a. This is based on the unpublished, phase 2a, randomized trial (COSMOS) evaluating the combination of sofosbuvir plus simeprevir with or without weight based ribavirin for 12 or 24 weeks. Of the 80 null responders with a Metavir fibrosis stage of 2 or less, 79% to 96% achieved SVR. Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47), SVR4 was observed in 93% of the 15 patients in the ribavirin containing arm and 100% of the 7 participants in the ribavirin-free arm. SVR 12 data is not yet available for this cohort of patients. This should not be used in those who had previous treatment with either telaprevir or boceprevir.

2. Alternative regimens include daily sofosbuvir for 12 weeks and PR for 12-24 weeks (Class IIB, Level C recommendation).
   a. The alternative regimen is based on very limited data, including a poor quality, single arm, open-label trial (NEUTRINO) that evaluated 12 weeks of sofosbuvir in treatment-naive subjects. Although treatment-experienced subjects were not included in this study, FDA estimates that the response rate in such patients would approximate the observed response rate in those in the NEUTRINO trial with baseline factors traditionally associated with a lower response to interferon-based treatment.

3. Alternative regimen includes simeprevir for 12 weeks plus PR for 48 weeks; all patients with cirrhosis who are receiving simeprevir should have well compensated liver disease (Class IIA, Level A recommendation).
   a. The ASPIRE trial is a phase 2b recently published trial evaluating simeprevir + PR in patients who had previously failed to respond to dual therapy. SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17).
4. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).

**Genotype 2, nonresponders**
1. Sofosbuvir + ribavirin for 12 weeks; patients with cirrhosis may benefit by extension of treatment to 16 weeks (Class 1, Level A recommendation).
2. Sofosbuvir + PR for 12 weeks (Class IIa, Level B recommendation).
   a. The LONESTAR-2 trial is an unpublished, open-label, single site, single-arm phase 2 trial evaluating triple therapy with sofosbuvir in treatment-experienced patients with HCV genotype 2 or 3.

**Genotype 3, nonresponders**
1. Sofosbuvir plus ribavirin for 24 weeks (Class IIa, Level A recommendation)
2. Alternative regimen includes retreatment with sofosbuvir + PR for 12 weeks.

**EASL Clinical Practice Guidelines:**
In December 2013, the European Association for the Study of the Liver (EASL) updated its HCV treatment guidelines. These guidelines were developed by a panel of experts and peer-reviewed by external expert reviewers. They were established using evidence and when not available, experts’ experiences and opinion. The GRADE system was used to evaluate the strength of recommendations. These guidelines did not include the new agents, sofosbuvir and simeprevir, and are therefore outdated. Relevant guidelines regarding initiation of therapy are included as follows:

- All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (recommendation A1).
- Treatment should not be deferred for patients with significant fibrosis, METAVIR score F3 to F2 (recommendation A1).
- In patients with less severe disease, the indication for and timing of therapy can be individualized (recommendation B1).

**Simeprevir and Sofosbuvir Combination Therapy:**
There is one small unpublished phase IIa study (COSMOS) evaluating the combination of simeprevir and sofosbuvir in the treatment of previous null responders and treatment naïve patients. Currently, only the abstract is available. The study is an open-label, randomized, phase II study in genotype 1 patients (n=167) with METAVIR scores F0-F2 who were prior null responders to PR (Cohort 1) or treatment-naïve patients and prior null responders with F3-F4 (Cohort 2). Patients in both cohorts were also randomized to simeprevir + sofosbuvir (with or without ribavirin for 12 weeks of simeprevir + sofosbuvir (with or without ribavirin) for 24 weeks. SVR 12 rates in the F0-F2 groups ranged from 79.2% to 96.3%. The lowest SVR 12 was in the most intense (24 weeks of the combination with ribavirin) treatment group and appears to be due to patients lost to follow-up, but the details of the data are not clear at this point. The highest SVR12 rate was in the simeprevir + sofosbuvir + ribavirin for 12 weeks group and SVR 12 was only 88.9% in those with the Q80K polymorphism. The results in the Cohort 2 patients with METAVIR F3-F4 fibrosis scores have not been released yet, although the preliminary SVR4 rates appear high. This preliminary data suggests that there may be no benefit from adding ribavirin to simeprevir and sofosbuvir and that 12 weeks of treatment may result in similar benefits compared to 24 week treatment. The most common adverse events were fatigue, headache, and nausea and anemia occurred mostly in the ribavirin-containing treatment groups.
Randomized Controlled Trials:
Seven potentially relevant RCTs were evaluated from the literature search. After further review, 2 RCTs\(^8,9\) included drugs not yet FDA approved and were therefore excluded, and one was a phase I study of boceprevir in HCV 2 and 3 genotype isolates assays and was also excluded.\(^10\) The remaining 4 RCTs are briefly described in the table below. Abstracts of these trials are found in Appendix 2:

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeuzem et al.(^14) RCT, Phase IIb, DB, PC</td>
<td>Simeprevir 12-48 weeks + PR vs. PR x 48 weeks</td>
<td>HCV genotype 1, non-responders to dual therapy with peginterferon and ribavirin</td>
<td>SVR at week 24 (SVR24)</td>
<td>SVR24&lt;br&gt;(\text{SIM}: 60.6%-80%)&lt;br&gt;P&lt;0.001&lt;br&gt;(\text{Pla}: 22.7%)&lt;br&gt;(\text{P}&lt;0.001)&lt;br&gt;Null responders: (\text{SIM}: 37.5%-58.8%)&lt;br&gt;(\text{Pla}: 18.8%)&lt;br&gt;Relapsers (\text{SIM}: 76.9%-88.9%)&lt;br&gt;(\text{Pla}: 37%)</td>
</tr>
<tr>
<td>Liu et al.(^11) Open-label, RCT</td>
<td>Pegylated interferon-alfa2a plus ribavirin vs. pegylated interferon alfa2a monotherapy x 48 weeks (n=205)</td>
<td>Treatment-naive patients with HCV genotype 1 receiving hemodialysis</td>
<td>SVR24</td>
<td>Peg + Rib: 66/103 (64%)&lt;br&gt;Peg alone: 34/102 (33%)&lt;br&gt;RR 1.92; 95% CI 1.41-2.62&lt;br&gt;P&lt;0.001</td>
</tr>
<tr>
<td>Rodriguez-Torres et al.(^12), RCT, DB, dose-ranging</td>
<td>Sofosbuvir (100, 200, or 400 mg) vs. placebo + PR x 28 days, followed by 44 weeks of PR alone</td>
<td>Treatment-naive, HCV genotype 1, non-cirrhotic</td>
<td>SVR24</td>
<td>Sof 100: 56%&lt;br&gt;Sof 200: 83%&lt;br&gt;Sof 400: 80%&lt;br&gt;PR: 43%&lt;br&gt;Peg alone: 34/102 (33%)&lt;br&gt;RR 1.92; 95% CI 1.41-2.62&lt;br&gt;P&lt;0.001</td>
</tr>
<tr>
<td>Benhamou et al.(^13) Phase 2a, partially blinded, RCT</td>
<td>Telaprevir 750 mg every 8 hours vs. telaprevir + PR vs. PR + placebo x 15 days (n=24)</td>
<td>Treatment-naive, HCV genotype 4</td>
<td>The effect of telaprevir on early viral kinetics</td>
<td>SVR at the end of treatment&lt;br&gt;Telaprevir: 62.5%&lt;br&gt;Telaprevir + PR: 50%&lt;br&gt;PR: 62.5%</td>
</tr>
</tbody>
</table>

Ongoing Trials:
A randomized trial comparing simeprevir to telaprevir in treatment-experienced patients is underway. This will be the first study to compare the new DAAs to the current standard of care for treating HCV genotype 1.\(^1\)
References:


Appendix 1: Prior authorization Criteria

**Sofosbuvir (Sovaldi®)**

**Goal(s):**
- Approve treatments of chronic hepatitis C which are supported by the medical literature and where there is medical evidence of effectiveness and safety

**Length of Authorization**
- Initial trial of 12 weeks
- Continuation of therapy up to 24-48 weeks of total therapy based on therapy regimen, genotype, and patient population

**Requires PA:**
- Sofosbuvir

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes: Go to</th>
<th>No: Pass to RPh, Deny For Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:</td>
<td>Go to #2</td>
<td></td>
</tr>
<tr>
<td>2. Is the request for continuation of therapy?</td>
<td>Go to “Continuation of Therapy”</td>
<td>Go to #3</td>
</tr>
<tr>
<td>3. What Hepatitis C genotype is the patient? Record Genotype:</td>
<td>Record Genotype and go to #4</td>
<td></td>
</tr>
<tr>
<td>4. Is the patient being prescribed the appropriate concomitant therapy based on genotype as seen in the dosage and administration table on the next page?</td>
<td>Go to #5</td>
<td></td>
</tr>
<tr>
<td>5. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?</td>
<td>Go to #6</td>
<td></td>
</tr>
<tr>
<td>6. If the patient has been treated with peginterferon and ribavirin before, do they have documented noncompliance to their previous treatment?</td>
<td>Pass to RPh, Deny For Appropriateness</td>
<td>Go to #7</td>
</tr>
<tr>
<td>7. Does the patient have a biopsy or other non-invasive technology (Fibroscan) to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).</td>
<td>Go to #8</td>
<td></td>
</tr>
<tr>
<td>8. Does the patient have a Child-Pugh score &lt; 7 (compensated liver disease)?</td>
<td>Go to #9</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>9. Does the patient have a HIV coinfection?</td>
<td>Go to #10</td>
<td>Go to #11</td>
</tr>
<tr>
<td>10. Is the patient under the supervision of an HIV specialist?</td>
<td>Go to #11</td>
<td>Pass to RPh; Deny (medical appropriateness)</td>
</tr>
<tr>
<td>11. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?</td>
<td>Go to #12</td>
<td>Pass to RPh, Deny for appropriateness</td>
</tr>
</tbody>
</table>

12. Does the patient have any of the following contraindications to therapy? Yes: Pass to RPh; Deny for No: Go to #13
- Severe or uncontrolled psychiatric disorder
- Decompensated cirrhosis
- Pregnancy

<table>
<thead>
<tr>
<th>13. Does the patient have significant renal impairment (CrCl &lt; 30 ml/min) or end stage renal disease (ESRD)?</th>
<th>Yes: Pass to RPh; Deny for appropriateness</th>
<th>No: Go to #14</th>
</tr>
</thead>
</table>

| 12. Is the request for sofosbuvir 400 mg daily? | Yes: Approve for 12 weeks for initial therapy. | No: Pass to RPh; Deny for appropriateness |

P&T Board Action: 1/30/13 (MH)
Revision(s): 3/27/13
Initiated:

### Continuation of Therapy - Sofosbuvir

Has the patient been adherent to and tolerated initial therapy?

| Yes: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below). If patient is awaiting liver transplantation, approve for up to additional 24 weeks or until liver transplantation, whichever occurs first. | No: DENY (Medical Appropriateness) |

### Dosage and Administration:

<table>
<thead>
<tr>
<th>Genotype 1 and 4</th>
<th>Sofosbuvir + peginterferon alfa + ribavirin</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td>Sofosbuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 3*</td>
<td>Sofosbuvir + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 1 and interferon ineligible</td>
<td>Sofosbuvir + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Those with hepatocellular carcinoma awaiting liver transplantation</td>
<td>Sofosbuvir + ribavirin</td>
<td>Up to 48 weeks or until liver transplantation, whichever occurs first</td>
</tr>
</tbody>
</table>

*Certain patients with genotype 3 (nonresponders with advanced fibrosis) can also be treated with sofosbuvir + peginterferon alfa + ribavirin for 12 weeks if deemed appropriate by physician.
## Hepatitis C Oral Protease Inhibitors/Triple Therapy

### Goal(s):
- Approve treatments of chronic hepatitis C which are supported by the medical literature

### Length of Authorization
- Initial trial of 8-12 weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

### Requires PA:
- Telaprevir
- Boceprevir
- Simeprevir

### Approval Criteria

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:</td>
<td>Go to #2</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>2.</td>
<td>Does the patient have documented HCV genotype 1? Record Genotype:</td>
<td>Go to #3</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>3.</td>
<td>Is the prescription for simeprevir?</td>
<td>Go to #4</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>4.</td>
<td>Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?</td>
<td>Go to #5</td>
<td>Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.</td>
</tr>
<tr>
<td>5.</td>
<td>Does the patient have the genotype 1 Q80K polymorphism virus?</td>
<td>Pass to RPh, Deny for Appropriateness</td>
<td>Go to #6</td>
</tr>
<tr>
<td>6.</td>
<td>Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?</td>
<td>Go to #7</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>7.</td>
<td>Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)</td>
<td>Go to “Continuation of Therapy”</td>
<td>Go to #8</td>
</tr>
<tr>
<td>8.</td>
<td>Does the patient have a Child-Pugh score &lt; 7 (compensated liver disease)?</td>
<td>Go to #9</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>9.</td>
<td>Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?</td>
<td>Go to #10</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
<tr>
<td>10.</td>
<td>If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?</td>
<td>Go to #11</td>
<td>Pass to RPh, Deny For Appropriateness</td>
</tr>
</tbody>
</table>
11. Does the patient have a biopsy to indicate moderate to severe fibrosis (Metavir score of 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins)?

| Yes: Go to #12 | No: Pass to RPh, Deny For Appropriateness |

12. Does the patient have a HIV coinfection?

| Yes: Go to #13 | No: Go to #14 |

13. Is the patient under the supervision of an HIV specialist?

| Yes: Go to #14 | No: Pass to RPh; Deny (medical appropriateness) |

14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?

| Yes: Pass to RPh, Deny for appropriateness | No: Go to #15 |

15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?

| Yes: Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks | No: Go to #16 (If dose is different pass to RPh for appropriateness) |

16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?

| Yes: Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response | No: Go to #17 (If dose is different pass to RPh for appropriateness) |

17. Is the request for simeprevir 150 mg once daily for 12 weeks?

| Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks | No: Pass to RPh; Deny for appropriateness |

---

**Continuation of Therapy- Telaprevir**

<table>
<thead>
<tr>
<th>1. Is the patient treatment-naive or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?</th>
<th>Yes: Approve as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavirin for 12 weeks (total treatment duration of 24 weeks).</td>
<td>No: DENY (Medical Appropriateness)</td>
</tr>
<tr>
<td>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Is the patient treatment-naive or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12</th>
<th>Yes: Approve as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavirin for additional 36 weeks (total treatment duration of 48 weeks).</td>
<td>No: DENY (Medical Appropriateness)</td>
</tr>
<tr>
<td>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.</td>
<td></td>
</tr>
</tbody>
</table>
3. Is the patient a prior partial or null responder?

<table>
<thead>
<tr>
<th><strong>Yes:</strong> Approve as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavirin for additional 36 weeks (total treatment duration of 48 weeks).</td>
</tr>
</tbody>
</table>

| **No:** DENY (Medical Appropriateness) |

4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?

<table>
<thead>
<tr>
<th><strong>Yes:</strong> Approve as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavirin for additional 36 weeks (total treatment duration of 48 weeks).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>No:</strong> DENY (Medical Appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.</td>
</tr>
</tbody>
</table>

*TREATMENT FUTILITY RULES*

Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks)

Week 24: Detectable Discontinue peginterferon and ribavirin.

If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued

**Continuation of Therapy- Boceprevir**

1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?

<table>
<thead>
<tr>
<th><strong>Yes:</strong> Approve as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)</td>
</tr>
</tbody>
</table>

| **No:** DENY (Medical Appropriateness) |

2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?

<table>
<thead>
<tr>
<th>Yes: Approve as follows:</th>
<th>No: DENY (Medical Appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)</td>
<td></td>
</tr>
</tbody>
</table>

3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?

<table>
<thead>
<tr>
<th>Yes: Approve as follows:</th>
<th>No: DENY (Medical Appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)</td>
<td></td>
</tr>
</tbody>
</table>

4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?

<table>
<thead>
<tr>
<th>Yes: Approve as follows:</th>
<th>No: DENY (Medical Appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)</td>
<td></td>
</tr>
</tbody>
</table>

5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?

<table>
<thead>
<tr>
<th>Yes: Approve as follows:</th>
<th>No: DENY (Medical Appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).</td>
<td></td>
</tr>
</tbody>
</table>

*TREATMENT FUTILITY RULES
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

**Continuation of Therapy- Simeprevir:** Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy.
1. Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4?

**Yes:** Approve as follows:
- Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavirin for 12 weeks (total treatment duration of 24 weeks).

**No:** DENY (Medical Appropriateness)

It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.

2. Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4?

**Yes:** Approve as follows:
- Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavirin for 36 weeks (total treatment duration of 48 weeks).

**No:** DENY (Medical Appropriateness)

It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.

*TREATMENT FUTILITY RULES*
If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.

* P&T Board Action: 1-26-2012
### Interferons and Ribavirins

**Goal(s):**
- Cover drugs only for those clients where there is medical evidence of effectiveness and safety

**Length of Authorization:** 16 weeks plus 12-36 additional weeks or 12 months

**Requires pa:** All drugs in HIC3 = W5G

**Preferred Alternatives:** See PDL list at: [http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml](http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml)

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes:</th>
<th>No:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is peginterferon requested preferred?</td>
<td>Go to #4</td>
<td>Go to #2.</td>
</tr>
<tr>
<td>3. If the request is for interferon alfacon-1, does the patient have a documented trial of a pegylated interferon?</td>
<td>Go to #4.</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
</tr>
<tr>
<td>4. Is the request for treatment of Chronic Hepatitis C?</td>
<td>Go to #5.</td>
<td>Go to #11</td>
</tr>
<tr>
<td>5. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)</td>
<td>Go to “Continuation of Therapy”</td>
<td>Go to #6</td>
</tr>
<tr>
<td>6. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment?</td>
<td>Forward to DMAP Medical Director</td>
<td>Go to #7</td>
</tr>
<tr>
<td>7. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy?</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
<td>Go to #8</td>
</tr>
</tbody>
</table>

- Severe or uncontrolled psychiatric disorder
- Decompensated cirrhosis or hepatic encephalopathy
- Hemoglobinopathy
- Untreated hyperthyroidism
- Severe renal impairment or transplant
- Autoimmune disease
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?</td>
<td>Go to #9</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
</tr>
<tr>
<td>9. Does the patient have a detectable HCV RNA (viral load) &gt; 50IU/mL? Record HCV RNA and date:</td>
<td>Go to #10</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
</tr>
<tr>
<td>10. Does the patient have a documented HCV Genotype? Record Genotype:</td>
<td>Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
</tr>
<tr>
<td>11. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?</td>
<td>Go to #11</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
</tr>
<tr>
<td>12. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?</td>
<td>Deny; Pass to RPH (Medical Appropriateness)</td>
<td>Go to #12</td>
</tr>
<tr>
<td>13. Has the member received previous treatment with pegylated interferon?</td>
<td>Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)</td>
<td>Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).</td>
</tr>
</tbody>
</table>

Continuation of Therapy- HCV
1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

**Yes:** Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Approve for</th>
<th>Apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 4</td>
<td>An additional 36 weeks or for up to a total of 48 weeks of therapy ( whichever is the lesser of the two).</td>
<td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).</td>
</tr>
<tr>
<td>2 or 3</td>
<td>An additional 12 weeks or for up to a total of 24 weeks of therapy ( whichever is the lesser of the two).</td>
<td>Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).</td>
</tr>
<tr>
<td>For all genotypes and HIV co-infection</td>
<td>An additional 36 weeks or for up to a total of 48 weeks of therapy ( whichever is the lesser of the two)</td>
<td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).</td>
</tr>
</tbody>
</table>

**No:** DENY (Medical Appropriateness)

Treatment with pegylated interferon-ribavirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

### Clinical Notes:
- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 ($10^5$) and 10,000,000 ($10^7$) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a "low level" of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml. (5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.

<table>
<thead>
<tr>
<th>Stage is indicative of fibrosis:</th>
<th>Grade is indicative of necrosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>None</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Enlargement of the portal areas by fibrosis</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Fibrosis extending out from the portal areas with rare bridges between portal areas</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Fibrosis that link up portal and central areas of the liver</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following are considered investigational and/or do not meet medical necessity criteria:

☑ Treatment of HBV or HCV in clinically decompensated cirrhosis
☑ Treatment of HCV or HBV in liver transplant recipients
☑ Treatment of HCV or HBV > 48 weeks
☑ Treatment of advanced renal cell carcinoma
☑ Treatment of thrombocytopenia
☑ Treatment of human papilloma virus
☑ Treatment of multiple myeloma
Appendix 2: Abstracts of potentially relevant RCTs


**Background & Aims:** Simeprevir (TMC435) is an oral NS3/4 protease inhibitor in phase III trials for chronic hepatitis C virus (HCV) infection. We performed a phase IIb, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the combination of simeprevir, peginterferon-α2a (PegIFN), and ribavirin (RBV) in patients with HCV genotype-1 infection previously treated with PegIFN and RBV.

**Methods:** We analyzed data from patients who did not respond (null response), had a partial response, or relapsed after treatment with PegIFN and RBV, randomly assigned to receive simeprevir (100 or 150 mg, once daily) for 12, 24, or 48 weeks plus PegIFN and RBV for 48 weeks (n = 396), or placebo plus PegIFN and RBV for 48 weeks (n = 66). All patients were followed for 24 weeks after planned end of treatment; the primary end point was the proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at that time point.

**Results:** Overall, rates of SVR at 24 weeks were significantly higher in the groups given simeprevir than those given placebo (61%–80% vs 23%; P < .001), regardless of prior response to PegIFN and RBV (simeprevir vs placebo: prior null response, 38%–59% vs 19%; prior partial response, 48%–86% vs 9%; prior relapse, 77%–89% vs 37%). All groups had comparable numbers of adverse events; these led to discontinuation of simeprevir or placebo and/or PegIFN and RBV in 8.8% of patients given simeprevir and 4.5% of those given placebo.

**Conclusions:** In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks PegIFN and RBV significantly increased rates of SVR at 24 weeks compared with patients given placebo, PegIFN, and RBV and was generally well tolerated.


**BACKGROUND:** Data are limited on the efficacy and safety of pegylated interferon plus ribavirin for patients with hepatitis C virus genotype 1 (HCV-1) receiving hemodialysis.

**OBJECTIVE:** To compare the efficacy and safety of combination therapy with pegylated interferon plus low-dose ribavirin and pegylated interferon monotherapy for treatment-naive patients with HCV-1 receiving hemodialysis.

**DESIGN:** Open-label, randomized, controlled trial. (ClinicalTrials.gov: NCT00491244).

**RESULTS:** Compared with monotherapy, combination therapy had a greater sustained virologic response rate (64% vs. 33%; relative risk, 1.92 [95% CI, 1.41 to 2.62]; P < .001). More patients receiving combination therapy had hemoglobin levels less than 8.5 g/dL than those receiving monotherapy (72% vs. 6%; risk difference, 66% [CI, 56% to 76%]; P < .001). Patients receiving combination therapy required a higher dosage (mean, 13 946 IU per week [SD, 6449] vs. 5833 IU per week [SD, 1169]; P = 0.006) and longer duration (mean, 29 weeks [SD, 9] vs. 18 weeks [SD, 7]; P = 0.004) of epoetin-β than patients receiving monotherapy. The adverse event-related withdrawal rates were 7% in the combination therapy group and 4% in the monotherapy group (risk difference, 3% [CI, -3% to 9%]).

**CONCLUSION:** In treatment-naive patients with HCV-1 receiving hemodialysis, combination therapy with pegylated interferon plus low-dose ribavirin achieved a greater sustained virologic response rate than pegylated interferon monotherapy.

BACKGROUND & AIDS: Sofosbuvir (formerly GS-7977) is a pyrimidine nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase. We assessed the safety, tolerability, antiviral activity, and pharmacokinetics of sofosbuvir plus pegylated-interferon (PegIFN)/ribavirin (RBV) in a 28-day, dose-ranging trial in treatment-naïve patients infected with genotype 1 HCV.

METHODS: In this double-blind study, 64 patients were randomized (1:1:1:1) to receive one of three once-daily doses of oral sofosbuvir (100, 200, or 400mg) or placebo plus PegIFN/RBV for 28 days, after which all patients continued to receive PegIFN/RBV alone for a further 44 weeks.

RESULTS: Patients in the sofosbuvir/PegIFN/RBV groups experienced mean reductions in HCV RNA >5 log_{10} IU/ml (-5.3 for 100 mg, -5.1 for 200 mg and -5.3 for 400 mg) vs. -2.8 log_{10} IU/ml for placebo/PegIFN/RBV after 28 days. Rapid virologic response (RVR) rates were markedly higher after sofosbuvir treatment (88-94%) than placebo (21%), as were rates of sustained virologic response (SVR) at post-treatment Week 24 (56%, 83%, and 80% for sofosbuvir 100, 200, and 400 mg, respectively, vs. 43% for placebo). The number of patients experiencing virologic breakthrough and post-treatment relapse was higher in the sofosbuvir 100 mg group than sofosbuvir 200 and 400 mg groups. Sofosbuvir was well tolerated; the most frequent adverse events were fatigue and nausea.

CONCLUSIONS: These results support further studies with sofosbuvir at 200 mg and 400 mg to determine the optimal dose and treatment duration of sofosbuvir in HCV genotype 1.


BACKGROUND: This partially blinded, randomized, phase 2a C210 study evaluated the antiviral activity of telaprevir-based regimens in treatment-naïve patients with chronic hepatitis C virus (HCV) genotype 4 infection.

METHODS: Twenty-four patients received telaprevir 750 mg every 8 hours for 15 days (T; n = 8), telaprevir in combination with pegylated interferon alfa-2a and ribavirin (Peg-IFN/RBV) for 15 days (TPR; n = 8), or Peg-IFN/RBV plus placebo for 15 days (PR; n = 8), followed by Peg-IFN/RBV for 46 or 48 weeks. The primary objective was to assess the effect of telaprevir on HCV RNA levels.

RESULTS: HCV RNA levels decreased slightly with T and PR; TPR produced substantial, rapid declines. On day 15, median reductions in the HCV RNA load from baseline were -0.77, -4.32, and -1.58 log_{10} IU/mL for T, TPR, and PR, respectively, and 0 patients in the T group, 1 in the TPR group, and 0 in the PR group had undetectable HCV RNA. Five of 8 patients who received telaprevir monotherapy had viral breakthrough within 15 days of treatment. Adverse event incidence was similar across treatments and comparable with the incidences from previous clinical trials. One patient (in T group) had a serious adverse event (considered unrelated to telaprevir) that led to treatment discontinuation.

CONCLUSIONS: Telaprevir with Peg-IFN/RBV had greater activity than Peg-IFN/RBV treatment or telaprevir monotherapy against HCV genotype 4. Telaprevir was generally safe and well tolerated. Further investigation of telaprevir combination therapy in patients with HCV genotype 4 infection is warranted.
Abbreviated Class Evaluation: Multivitamins and Antioxidants

Month/Year of Review: March 2014
End date of literature search: February 2014
Current PDL Class: None

Research Questions:
- Is there evidence to support and cover the use of specific products with good value, including multivitamins, iron products, and mono-vitamin supplements?
- Are certain reformulations of vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?

Conclusions:
- Based on a high quality systematic review of patients with cardiovascular disease (CVD), there is insufficient evidence for commonly used supplements (vitamin E, coenzyme Q10, magnesium) used by patients with CVD in terms of efficacy and harms on long term clinical outcomes (mortality, thrombotic events, and serious adverse events). Low-strength evidence suggests benefits of vitamin K (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes.¹
- Based on a high quality systematic review in the general population, there is moderate quality evidence of no benefit on all-cause mortality (RR 0.95; 95% CI 0.81-1.11) or cardiovascular disease (CVD) with a multivitamin in nutrient-sufficient adults and evidence that beta-carotene, vitamins A, C, D, and E; selenium, folic acid, and calcium have no benefit on CVD, cancer or all-cause mortality. There is insufficient evidence to evaluate the B vitamins (1, 2, 6 and 12) on CVD, cancer, or all-cause mortality outcomes.² Another systematic review demonstrated no difference in mortality with antioxidants in adults (RR 1.02; 95% CI 0.98-1.05) and a significantly higher mortality with beta-carotene (RR 1.05; 95% CI 1.01-1.09) and vitamin E (RR 1.03; 95% CI 1.00-1.05).³
- There is insufficient and conflicting evidence that multivitamin supplementation in men may lower cancer incidence (RR 0.93; 95% CI 0.87-0.99; NNT 98 over 11.2-12.5 years) but no effect in women. This suggests a small reduction in overall cancer incidence in men with a multivitamin after 11.2 to 12.5 years of follow-up (HR 0.92; 95% CI 0.86-0.998; NNT 82-131).²
• In another fixed effects meta-analysis, vitamin or antioxidant supplements were not associated with a reduced risk of major CV events (RR 1.00; 95% CI 0.98-1.02) for primary or secondary prevention.4
• There is high quality evidence of no beneficial effect on CVD, cancer, or all-cause mortality with vitamin E supplementation in the general population.
• There is high quality evidence that supplementation with beta-carotene increases the risk of lung cancer in those at high risk.
• Oral iron therapy remains first line treatment for iron deficiency anemia. These include the ferrous salts, such as ferrous fumarate, ferrous sulfate, and ferrous gluconate. Due to no evidence of a difference in efficacy, evaluate comparative costs in executive session for preferred products.
• There is moderate quality evidence, based on 2 systematic reviews, that homocysteine-lowering B vitamins do not reduce the risk for overall mortality or myocardial infarction.5,6 Evidence is more conflicting for its effects on risk of stroke.
• The evidence is insufficient and conflicting to support the use of vitamin E for treatment of Alzheimer’s disease (AD).

Recommendations:
• Based on evidence of no benefit in mortality, CVD, or cancer outcomes, consider adding multivitamins and antioxidant multivitamins to the exclusion list.
• For other supplements with evidence to support their use or insufficient evidence to make conclusions, evaluate comparative costs in executive session due to no evidence of superiority of individual products over another. This includes calcium, vitamin D, folic acid, vitamin B formulations, and the ferrous salt formulations.
• Bring back review of other minerals and electrolytes for similar decision-making.

Background:
Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.1 This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements.7 Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.8 While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies, particularly vitamin A and iron deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.9

There has been contradictory evidence for potential role of vitamin D and omega-3 fatty acids in the prevention of cancer and cardiovascular disease (CVD) and large gaps remain in the current evidence. The large Women’s Health Initiative trial randomized 36,282 postmenopausal women to a daily combination of calcium and low-dose vitamin D3 or to placebo for a mean of 7 years. Results showed that the vitamin combination did not reduce the risk for cancer, CHD, or
stroke, and its effect on 25(OH)D levels was small.\textsuperscript{10,11} However, there are no RCT’s evaluating vitamin D doses large enough to produce substantial changes in 25(OH)D levels. The ongoing VITamin D and OmegA-3 Trial (VITAL) is a large 5 year RCT designed to assess the role of vitamin D and omega-2 fatty acids in the primary prevention of cancer and CVD.\textsuperscript{11}

Iron deficiency is the most common nutritional disorder worldwide and oral iron therapy can be used first line as supplemental iron, including in pregnant women and children.\textsuperscript{12} Adherence to oral iron therapy can be a barrier to treatment because of gastrointestinal adverse effects. Many preparations are available, varying widely in dosage, formulation (quick or prolonged release), and chemical state (ferrous or ferric form). The World Health Organization recommends the use of ferrous salts, which are considered the most effective and cost-effective treatment and preferred to ferric supplements, which show poorer absorption.\textsuperscript{13} Delayed release formulations have been developed to attempt to alleviate some of the gastrointestinal intolerances. The incidence of gastrointestinal side effects has been shown to be lower with controlled-release iron formulations, however; none have showed a difference in the discontinuation rates between them.

**Methods:**
A Medline literature search ending June 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for the following dietary and vitamin groups was conducted: vitamins A, B, C, D and E, multivitamin preparations, antioxidant vitamins, vitamin B12, folic acid, and iron replacement therapy. Omega-3 fatty acids were excluded, as these were evaluated in a separate P&T review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

**Efficacy Summary:**

**Systematic Reviews:**

1. A systematic review by Marik, et. Al evaluated the benefits and risks of dietary supplements in Westernized societies.\textsuperscript{9} They included RCTs in nonpregnant adults that evaluated clinical endpoints and were at least a year long. Sixty three studies were included that evaluated B-carotene, vitamins A, B6, B12, C, D, and E; folic acid, calcium, selenium, omega-3 fatty acids, glucosamine, saw palmetto, and milk thistle. Results of no benefit were shown in 45 studies, with 10 of these showing a trend toward harm and 2 showing a trend toward benefit. Beneficial results were reported in 12 studies; 6 studied vitamin D in elderly patients and 3 studied omega-3 fatty acids in patients with cardiovascular disease. The authors concluded that with the potential exceptions of vitamin D supplementation in the elderly and omega-3 fatty acid use in those with cardiovascular disease, there is no data to support the widespread use of dietary supplements in Westernized populations. In addition, certain commonly used supplements (B-carotene, vitamin A, and vitamin E) may be harmful.\textsuperscript{9}

2. A comparative effectiveness review by AHRQ evaluated the evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings.\textsuperscript{1} A total of 69 studies contributed to the meta-analysis; no systematic reviews were identified. Most of the evidence was
graded as insufficient and most had low statistical power due to short-term efficacy design. Strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events, limiting the generalizability of the results. The authors concluded that the many limitations of the evidence made it difficult to make meaningful conclusions for most supplement-drug combinations. Low-strength evidence suggests benefits of omega-3 fatty acids (incremental improvement of triglyceridemia), vitamin K, (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes. Evidence on harms was inconclusive. No evidence on clinical effectiveness outcomes was found for Echinacea, garlic, ginseng, niacin, red yeast, vitamin A, or vitamin D supplementation coadministered with a CV drug. No evidence on intermediate outcomes was identified for effects of vitamin A or vitamin D supplementation in combination with CV drugs. No study analyzed statistical interactions between a supplement and a CV drug in terms of clinical outcomes. Additional specific conclusions based on supplement type are as follows:

**Coenzyme Q10:** There is insufficient evidence to determine the effectiveness of the combination of a CV drug (ACE inhibitors) and coenzyme Q10 compared to placebo on all-cause mortality and quality of life. When evaluating intermediate cardiovascular outcomes, there was insufficient to low quality of evidence, based on 4 RCTs with unclear CHD risk, mixed CHD risk, and high CHD risk. Overall, no significant differences were demonstrated between coenzyme Q10 in combination with a cardiovascular drug versus drug alone in levels of the following: C-reactive protein, high-density lipoprotein (HDL) cholesterol, non-HDL-C, total cholesterol, triglycerides, ejection fraction, or systolic blood pressure. Low grade evidence from one trial concluded no significant differences in HDL-C with coenzyme Q10 in combination with fenofibrates versus fenofibrates alone.

**Vitamin E:** There was insufficient evidence evaluating Vitamin E in combination with cardiovascular drugs on clinical outcomes such as CV mortality. There were 10 RCTs that measured intermediate outcomes and examined its use with antiplatelet agents or statins. Also, evidence from a well-powered pragmatic trial in women showed no benefit of adding vitamin E to daily aspirin on the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death. There was insufficient evidence based on one small trial of no difference in total cholesterol and triglyceride levels between vitamin E in combination with an antiplatelet agent versus antiplatelet alone. There was low quality evidence that the combination of vitamin E and nifedipine significantly lowered total cholesterol (MD -35.96 mg/dl, 95% CI -46.96 to -24.96), LDL, and triglycerides, but not HDL or systolic blood pressure in 30 elderly patients at high risk of CHD. There was no significant difference in lipid profile in trials with vitamin E and gemfibrozil or vitamin E-statin combinations (insufficient evidence). There was also no significant difference in blood pressure, C reactive protein, prothrombin time, and platelet count for vitamin E-statin combinations versus cardiovascular drugs alone.

**Vitamin K:** There was insufficient evidence to evaluate mortality and stroke when vitamin K was coadministered with warfarin. There is low quality evidence that supplementation with vitamin K may improve the stability of warfarin therapy. One trial showed that the percentage of time INR was in therapeutic range was improved in the group receiving vitamin K in combination with warfarin compared to warfarin alone (RR 9.0, 95% CI 1.42 to 16.57). The number of patients achieving stable INR was also higher in the combination group (RR 2.56, 95% CI 1.24 to 5.38).

**Magnesium:** There was insufficient evidence of no difference in myocardial infarction between oral magnesium + beta-blockers compared to beta-blockers alone. Three RCTs evaluated intermediate outcomes with magnesium in combination with hydrochlorothiazide or beta-blockers in participants with hypertension. In two trials, systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ significantly between the magnesium hydrochlorothiazide combinations versus hydrochlorothiazide-alone groups (insufficient evidence). There was also no significant difference with the combination of magnesium plus beta-blockers versus beta-blockers alone (insufficient evidence).
Multivitamins and Antioxidant Multivitamins:

3. A 2013 AHRQ systematic evidence review for the U.S. Preventive Services Task Force (USPSTF) evaluated the evidence for the use of multivitamins or single nutrients and functionally related nutrient pairs for the primary prevention of CVD and cancer in the general population with a generally adequate diet. Two total of 26 studies were ultimately included in the analysis, with 4 good-quality RCTs and one good-quality cohort study that evaluated the effects of a multivitamin supplement. No impact on all-cause mortality was found in any of the multivitamin RCTs reporting this outcome (RR 0.95; 95% CI 0.81-1.11). Two RCTs reported on CVD and cancer outcomes, and showed no impact on most types of fatal and nonfatal CVD events with the use of a multivitamin, with one trial reporting a small benefit for fatal MI. Both trials suggested a small reduction in overall cancer incidence in men after 11.2 to 12.5 years of follow-up (HR 0.92; 95% CI 0.86-0.998). Another trial showed no impact on overall cancer from a 5-component multivitamin. A subgroup analysis showed a protective effect on any cancer among men (RR 0.69; 95% CI 0.53 to 0.91), but not women. From the two trials, one cancer case would be prevented if 98 men used a daily multivitamin for 11.2 years (NNT 83) to 12.5 years (NNT 131). No consistent evidence of harms from multivitamins was observed from the four RCTs.

No trials reported incidence of CVD, cancer, or all-cause mortality for 4 B vitamins (1, 2, 6, and 12), iron, zinc, magnesium, niacin, calcium/magnesium, folic acid/vitamin B12, or folic acid/vitamin B6). Overall, the evidence for beta-carotene, vitamins A, C, D, and E; selenium; folic acid; calcium; and some combinations found no evidence for a benefit of the supplement on CVD, cancer, or all-cause mortality. Two studies of beta-carotene for those at high risk for lung cancer found that those in the supplement groups were at a significantly higher risk of developing or dying from lung cancer. For most supplements, there were a limited number of studies, with the exception of vitamin E, which included 6 fair- to good-quality trials that all produced no effects on the measured endpoints.

4. Another systematic review assessed the efficacy of vitamin and antioxidant supplements in the prevention of CV diseases through a meta-analysis of RCTs. Trials with at least 6 months of follow-up were included. Trials were assessed for quality using the Jadad scale. A total of 50 trials were included in the final analysis (294,478 participants). Thirty were primary prevention trials and 20 were secondary prevention trials. In the fixed effects meta-analysis of all 50 trials, use of vitamin or antioxidant supplements was not associated with reduced risk of major CV events (RR 1.00; 95% CI 0.98-1.02). The effect sizes of the smaller trials tended to be less than 1.0, while the larger ones tended to be null. Subgroup analysis, showed that low dose vitamin B₆ supplementation slightly decreased the risk of major CV events (RR 0.92; 95% CI 0.85-0.99) in the fixed effects meta-analysis. No significant association was found by type of outcome, type of prevention, type of study design, methodological quality, duration of treatment, funding source, and provider of the supplements. Vitamin E supplementation was associated with a decreased risk of myocardial infarction; however these beneficial effects were shown only in trials with supplements provided by the pharmaceutical industry.

5. Another systematic review evaluated only antioxidant vitamins (vitamin E, beta-carotene, and vitamin C) and their effect on CV outcomes. Published and unpublished randomized trials were included from the literature search. The 5-point Jadad score was used to evaluate the quality of the inclusive trials. A total of 29 articles were included in the meta-analysis. Trials with both participants with high CV risk factors or previous CV disease and individuals without CV risk factors. The overall meta-analysis demonstrated no effect on major CV events with antioxidant vitamin supplementation (RR 1.00; 95% CI 0.96-1.03; p=0.79) without evidence of heterogeneity of effect. Supplementation was shown to reduce the risk of myocardial infarction by 2%, but this different was not clinically or statistically significant (RR 0.98; 95% CI 0.92-1.04; p=0.54), with little heterogeneity. There was also no significant effect seen on stroke risk (RR 0.99; 95% CI 0.93-1.05; p=0.65) or total death (RR 1.03; 95% CI 0.98-1.07; p=0.22).
6. Authors recently looked to determine whether multivitamin-multimineral supplementation, used for primary or secondary prevention, increased the risk of mortality. Only RCTs were included and the primary outcome was all-cause mortality. Trials were assessed for internal validity using the Cochrane guidelines. After review, 21 studies met inclusion criteria and were included in the review (n=91,074). Four studies had either an unclear or high risk of bias. Across all pooled studies, no significant effect of supplementation on all-cause mortality was observed (RR 0.98; 95% CI 0.94-1.02) and there was little evidence of heterogeneity ($I^2=15.72\%$; $p=0.25$). Removal of the 4 studies with a high risk of bias did not significantly change the risk estimate. A trend towards a reduction in the risk of all-cause mortality was seen in the 13 primary prevention trials, and no significant effect was found in the secondary prevention trials (RR 1.04; 95% CI 0.98-1.11). Multivitamin supplementation had no effect on mortality due to vascular causes or cancer.

7. To assess the beneficial and harmful effects of antioxidant supplements for prevention of mortality in adults, a Cochrane systematic review and meta-analysis was done. The systematic review included 78 RCTs that evaluated antioxidants in adult participants from the general population (primary prevention), or were patients with stable, chronic diseases (Secondary prevention). Fifty six trials (82%) were considered to have a low risk of bias. A random effects meta-analysis showed neither a higher or lower mortality with antioxidant supplements (RR 1.02; 95% CI 0.98-1.05), but a fixed-effects meta-analysis showed a statistically significant higher mortality (RR 1.03; 95% CI 1.01-1.05). Heterogeneity between studies was low, with an $I^2$ of 12%. In the 56 trials with a low risk of bias, both the fixed-effect model and random-effects model meta-analyses showed that the antioxidants were associated with higher mortality (12.9% vs. 10.6%; RR 1.04; 95% CI 1.01 – 1.07). Beta-carotene (RR 1.05; 95% CI 1.01-1.09) and vitamin E (RR 1.00-1.05) were associated with significantly higher mortality, whereas vitamin A, vitamin C, and selenium were not associated with higher or lower mortality.

8. Another review also evaluated, multivitamin-multimineral use and CV disease and cancer incidence. Only prospective studies were included, however; this review did include observational trials in addition to interventional trials and only looked at supplementation in primary prevention among health adults. Studies included in the Macpherson systematic review were often excluded because they were conducted among nutritionally deficient populations. A total of 15 studies were included in the review. Twelve were prospective observational studies and only 3 were RCTs. A meta-analysis was not conducted by the authors. The author found that supplementation with multivitamin-multiminerals does not appear to increase all-cause mortality, cancer incidence or mortality, or CVD incidence or mortality. However, this is based mostly on observational data which is not as strong as data from RCTs.

9. The Department of Veterans Affairs Health Services Research and Development conducted a systematic review evaluating nutritional supplements for age related macular degeneration (AMD). A thorough literature search was conducted, internal validity of each study was assessed using the Cochrane Risk of Bias tool, and the overall quality of the body of evidence was evaluated using the GRADE method. A total of 38 articles met inclusion criteria for review. A total of 7 RCTs evaluated nutritional supplements in AMD patients. A significant effect in preventing functional loss was found only in the two largest trials (good evidence). The largest study included 3640 subjects and followed them for 7 years. In this study, a beneficial effect was observed with a combination of antioxidants (vitamin C, vitamin E, and beta carotene) plus zinc (OR 0.63; 99%CI 0.44-0.92), but only in subjects with Categories 3 and 4 AMD. No significant change was reported in mild AMD subjects. The evidence also showed that certain nutritional supplements have significant potential harms, including increased mortality and congestive heart failure in high risk patients with vitamin E, increased risk of prostate cancer with vitamin E, and increased risk of lung cancer among smokers with beta-carotene.
Vitamin D and Calcium:
According to DynaMed, calcium supplements are generally recommended for hypocalcemia, hypoparathroidism, and for the treatment and prevention of osteoporosis. There is level 2 evidence of reduced fracture risk with calcium supplementation and calcium plus vitamin D in older adults and level 3 evidence that calcium supplementation in postmenopausal women appears to improve bone density but effects on fracture remain uncertain.

10. A meta-analysis was done evaluating vitamin D supplementation and its effects on overall mortality. A literature search was conducted through January 2013, to identify RCTs, and trials were assessed for quality using the Cochrane Collaboration’s tool. A total of 42 RCTs that met inclusion criteria were included in the final analysis (n=85,466). Calcium supplementation was also used in 26 trials and the majority of participants were women. In the 29 trials with follow-up less than 3 years, vitamin D did not significantly decrease all-cause mortality in the vitamin D group compared to placebo (13.3% vs. 12.2%; RR 1.03; 95% CI 0.97-1.12; p=0.28; I²=12%). In the 13 trials with follow-up of 3 years or longer, data demonstrated a decrease in all-cause mortality in the vitamin D group compared to placebo (10.9% vs. 11.5%; RR 0.94; 95% CI 0.90-0.98; p=0.001; I²=0%). Results were similar when excluding the trials that had a high risk of bias. There is insufficient evidence to draw conclusions of the effect of vitamin D on specific mortality. The authors concluded that long term supplementation of vitamin D may have a beneficial effect on overall mortality (with a modest effect size), especially in patients with vitamin D insufficiency and younger than 80 years. Vitamin D in a dose of 800 IU daily or less was found to be more favorable than a dose greater than 800 IU and treatment with cholecalciferol was more favorable than ergocalciferol. Future studies are needed to evaluate the efficacy on specific mortality, such as cancer and CV disease.

11. A systematic review evaluated the evidence of RCTs to assess the efficacy of oral vitamin D supplementation in depression compared to placebo. The review was done in accordance to the Cochrane Handbook. After a literature search and review, 6 studies met the inclusion criteria and were included in the final meta-analysis. Results showed no significant effect of vitamin D supplementation on depression, with the standardized mean difference (SMD) of -0.14 (95% CI -0.41 to 0.13; p=0.32) and substantial heterogeneity (I²=77%; p=0.001). Two trials used a dichotomous outcome for response and these trials showed no overall effect of vitamin D supplementation on depression (OR 0.93; 95% CI 0.54 to 1.59; p=0.79). None of the subgroup analysis showed any significant effect of vitamin D supplementation on depression. A sensitivity analysis also showed no significant effect when excluding studies with a high risk of bias or short duration of intervention. No significant difference in adverse events was found between placebo and vitamin D groups.

12. A systematic review and meta-analysis evaluated whether vitamin D supplementation affects bone mineral density (BMD) due to recent data showing no effect of vitamin D supplementation on fracture prevention. Authors used the PRISMA guidelines to conduct the meta-analysis and only included RCTs. Studies of individuals with other disorders likely to affect bone and calcium metabolism (chronic kidney disease, pregnancy, glucocorticoid use) were not eligible. The primary endpoint was the percentage change in bone mineral density from baseline. There was a significant difference in the weighted mean difference (WMD) in femoral neck BMD (0.8; 95% CI 0.2-1.4; p=0.005), but with evidence of heterogeneity. There was no statistically significant effect on lumbar spine BMD (WMD 0.0; 95% CI -0.2 to 0.3; p=0.8), hip BMD (WMD 0.2; 95% CI -0.1 to 0.4; p=0.17), and total body BMD (WMD -0.3; 95% CI -0.7 to 0.1; p=0.2) with vitamin D supplementation. Meta-regression analysis showed no significant interactions between age, vitamin D concentration, sex, study duration, vitamin D dose, baseline BMD, or number of participants and BMD. The authors concluded that continuing widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seems to be inappropriate.

13. A 2013 draft systematic review was released by AHRQ on Vitamin D and Calcium and clinical outcomes. Based on the evidence, it was difficult to make any strong conclusions on the association of vitamin D supplementation, calcium intake, or the combination of both nutrients with the various health outcomes because most of the findings were inconsistent. Due to the large degree of clinical and methodological heterogeneity across studies, it was not possible to perform an updated meta-analysis.
Iron therapy:

14. A systematic review was conducted to analyze the tolerability of several oral iron supplements. Clinical or observational studies were including from a literature search through 2009. This review has many inherent limitations and therefore results need to be interpreted with caution. Individual trials were not assessed for quality and there were no restrictions on the type of clinical studies included. In total, 111 studies were included in the analysis. This analysis showed that extended-release ferrous sulfate had the lowest incidence of adverse events, and all other formulations were compared to it. Ferrous fumarate and ferrous sulfate were shown to have the highest rate of gastrointestinal adverse events. The heterogeneity of the studies was not evaluated or mentioned and it appears that the studies differed in terms of doses used, severity of iron deficiency, and study design.

Vitamin B:

15. A recent meta-analysis looked at the effect of Vitamin B supplementation and the risk of cerebrovascular disease. Only RCTs through August 2012 were included that compared B vitamins with placebo, very low-dose B vitamins, or usual care with a minimum follow-up time of 6 months. Fourteen articles (n=54,913) were included in the meta-analysis and were assessed for quality by two investigators. Results demonstrated a trend toward benefit of B vitamin intake to lower homocysteine levels and reduce stroke events (RR 0.93; 95% CI 0.86-1.00; p=0.05), but no benefit on specific subtypes such as transient ischemic attacks or myocardial infarction (RR 1.00; 95% CI 0.94-1.07; p=0.98) outcomes. Analyses specific to vitamin B12 did not show a significant benefit for reduction of stroke events. There was also no change in rates of morbidity and mortality of tumors in B vitamin groups (RR 1.05; 95% CI 0.98-1.11; p=0.17).

16. A recent meta-analysis evaluated the effect of vitamin B supplementation on stroke. From a comprehensive literature search, 18 RCTs met inclusion criteria. The studies compared B-vitamin supplementation to a placebo for reduction of incident stroke in patients with chronic kidney disease (7 trials), CV or stroke (8 trials) or healthy individuals (1 trial). Pooling the trials demonstrated that there was no evidence that B-vitamin supplementation protected against stroke risk (RR 0.91, 95% CI 0.82-1.01; p=0.075). No statistically significant heterogeneity was observed between trials for incident stroke ($I^2=22.8\%$). After excluding the trial that included patients with a glomerular filtration rate less than 50, vitamin-B supplementation was associated with a nonsignificant reduction in the risk of stroke (RR 0.91; 95% CI 0.83-1.00; p=0.06). Subgroup analysis suggested that B-vitamin supplementation might reduce the risk of stroke if included trials had a man/woman ratio of more than 2 or subjects received doses of folic acid less than 1 mg.

17. A Cochrane systematic review was conducted to assess the clinical effectiveness of homocysteine-lowering interventions in people with or without pre-existing cardiovascular disease. This review showed that homocysteine-lowering B vitamins (folic acid, B6, and/or B12) in patients at risk of CV disease do not reduce the risk for myocardial infarction or overall mortality and may not reduce the risk for stroke. Twelve RCTs were found of homocysteine-lowering vitamins in adults with risk of or established CV disease. Compared to placebo or standard care, there was no difference seen in myocardial infarction (RR 1.02; 95% CI 0.95-1.01), all-cause mortality (RR 1.01; 95% CI 0.96-1.07), or stroke (RR 0.91; 95% CI 0.82-1.01).

Vitamin E:

18. A systematic review from Cochrane Collaboration assessed the efficacy of Vitamin E for Alzheimer’s dementia (AD) and mild cognitive impairment (MCI). All RCTs comparing vitamin E to placebo for patients with either AD or MCI were included. Only three trials met the inclusion criteria. Two were trials of vitamin E for the treatment of AD and one was a trial of vitamin E to delay progression from amnestic MCI to dementia. All three had a low risk of bias. The two trials evaluating AD patients were not able to be pooled based on different outcome measures. One trial found no significant difference in survival time to one of the four end points between the vitamin E and placebo groups (RR=0.70; p=0.08) in patients with AD. The study in MCI patients found no
significant difference in the probability of progression from MCI to AD over the 3 years between the vitamin E group and placebo group (HR 1.02; 95% CI 0.74-1.41; p=0.91). The authors concluded that there was no strong evidence that vitamin E when compared to placebo was efficacious in improving outcomes of AD or MCI.

Clinical Guidelines

The Endocrine Society
Clinical Practice guidelines were updated in 2011 focusing those who are at risk for vitamin D deficiency. These guidelines were guided by systematic reviews of the evidence and consensus decisions. The task force used the GRADE approach to make evidence based recommendations. Strong recommendations include the phrase “we recommend” and weak recommendations use the phrase “we suggest”. Main recommendations are as follows:

- Recommend screening is only recommended in individuals at risk for vitamin D deficiency (high quality evidence). There is no evidence demonstrating benefits of screening for vitamin D deficiency at a population level.
- Measurement of 25(OH)D is reasonable in the following at risk groups:
  - Rickets, osteomalacia, osteoporosis, chronic kidney disease, hepatic failure, malabsorption syndromes, hyperparathyroidism, certain medications, African-American and Hispanic children and adults, pregnant and lactating women, older adults with a history of falls, older adults with a history of nontraumatic fractures, obese children and adults, granuloma-forming disorders, lymphomas

Recommended dietary intakes of vitamin D for patients at risk for vitamin D deficiency

- Infants and children aged 0-1 require at least 400 IU/d of vitamin D and children 1 year and older require at least 600 IU/d to maximize bone health; however, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1000 IU/d of vitamin D (weak recommendation; high quality evidence).
- Adults 19-50 years require at least 600 IU/d of vitamin D to maximize bone health and muscle function; however, to raise the blood level of 25(OH)D above 30 ng/ml may require at least 1500-2000 IU/d of vitamin D (weak recommendation, high quality evidence).
- All adults aged 50-70 and 70+ require at least 600 and 800 IU/d, respectively, of vitamin D to maximize bone health and muscle function. However, to raise the blood level above 30 ng/ml may require at least 1500-2000 IU/d of supplemental vitamin D (weak recommendation; high quality evidence).
- Pregnant and lactating women require at least 600 IU/d of vitamin D and at least 1500-2000 IU/d may be needed to maintain a blood level of 25(OH)D above 20 ng/ml (weak recommendations, moderate quality evidence).

Treatment and Prevention Strategies

- Either vitamin D2 or vitamin D3 should be used for the treatment and prevention of vitamin D deficiency (weak recommendation; high quality evidence).
- For children 1-18 years who are vitamin D deficient, the suggested treatment is 2000 IU/d of vitamin D for at least 6 weeks or with 50,000 IU of vitamin D2 once a week for at least 6 weeks followed by maintenance therapy of 600-1000 IU/d (weak recommendation; high quality evidence).
- All adults who are deficient should be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 week or its equivalent of 6000 IU/d, followed by maintenance therapy of 1500-2000 IU/d (weak recommendation; high quality evidence).
- Recommend prescribing vitamin D supplementation for fall prevention, but do not recommend prescribing supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (high quality evidence).
National Osteoporosis Foundation:

In 2013, the National Osteoporosis Foundation released a reference on the prevention, diagnosis and treatment of osteoporosis in the US. This guide addressed postmenopausal women and men age 50 and older using evidence mainly from RCTs. It is recommended that adequate daily calcium and vitamin D is ensured to help reduce fracture risk. If adequate dietary calcium cannot be obtained, dietary supplementation is indicated up to the recommended daily intake. They recommend with the IOM recommendations of 1000mg per day of calcium for men age 50-70 and 1200mg per day of calcium for women age 51 and older. Intakes in excess of 1200 to 15000 mg per day have limited potential for benefit and may increase the risk of developing kidney stones, CV disease, and stroke. They also recommend an intake of 800 to 1000 IU of vitamin D per day for adults age 50 and older. Adults who are vitamin D deficient may be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week or the equivalent daily dose for 8-12 weeks to achieve a 25(OH)D blood level of approximately 30 ng/ml.

U.S. Preventive Services Task Force (USPSTF): Multivitamins for primary prevention

In February 2014, the USPSTF released updated recommendations on multivitamins for the primary prevention of CV disease and cancer in healthy adults. The previous recommendations were from 2003 and concluded that the evidence at the time was insufficient to assess the balance of benefits and harms of the use of supplements of vitamins A, C or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer of CVD in asymptomatic adults. The new evidence was based on the AHRQ systematic review described above. The following is a summary of recommendations and evidence:

- The current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of CV disease or cancer (I statement).
- The current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (with the exception of beta-carotene and vitamin E) for the prevention of CV disease or cancer (I statement.)
  - Across all of the supplements studied (Vitamin A, vitamin C, vitamin D with or without Calcium, Vitamin E, Selenium, Folic acid), there was no evidence of beneficial effect on CV disease, cancer, or all-cause mortality. However, there were a limited number of studies for most nutrients and differences made pooling difficult. Therefore, they concluded that they were not able to conclude with certainty that there is no effect.
  - The USPSTF did conclude with moderate certainty that the net benefit of Beta carotene is negative, due to an increased risk for lung cancer and that the net benefit of vitamin E supplementation is zero due to no effect on CV disease, cancer, or all-cause mortality.
- The USPSTF recommends against the use of beta-carotene of vitamin E supplements for the prevention of CV disease or cancer (D recommendation). This is based on adequate evidence that supplementation with beta-carotene or vitamin E in healthy populations without nutritional deficiencies does not reduce the risk of CV disease or cancer.
- There is inadequate evidence on the harms of supplementation with multivitamins and most single vitamins, minerals, or functional pairs.
- There is adequate evidence that supplementation with vitamin E has little or no significant harms and that supplementation with beta-carotene increases the risk of lung cancer in persons who are at increased risk of lung cancer.

U.S. Preventive Services Task Force (USPSTF): Vitamin D and calcium supplementation

In 2013, the USPSTF released guidelines for Vitamin D and calcium supplementation to prevent fractures in adults. The USPSTF commissioned 2 systematic evidence reviews and a meta-analysis on supplementation to assess the effects on bone health outcomes in community-dwelling adults, the association of vitamin D and calcium levels with bone health outcomes, and the adverse effects of supplementation. They concluded that:

- The current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men (I statement).
- The evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D3 and greater than 1000 mg of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women (I statement).
The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D3 and 1000 mg or less of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women (D recommendation).

Vitamin D supplementation is effective in preventing falls in community-dwelling adults aged 65 years or older who are at increased risk for falls (B recommendation).

These recommendations are based on an AHRQ systematic review that examined the benefits and harms of vitamin D with or without calcium supplementation on clinical outcomes of cancer and fractures. Sixteen RCTs examined the effects of vitamin D with or without calcium supplements on fracture outcomes. Four of these were poor quality. A random effects meta-analysis with 5 RCTs showed no significant difference in total fracture between vitamin D supplementation and placebo (RR 1.03; 95% CI 0.84-1.26), with high heterogeneity across studies (I²=60%). Eleven RCTs compared the combination of vitamin D and calcium supplementation with placebo in mostly postmenopausal women and demonstrated a reduced risk for total fracture as compared with placebo (RR 0.88; 95% CI 0.78-0.99), with moderate heterogeneity (I²=36%). Subgroup analysis showed that the pooled effect estimated differed according to setting; the risk reduction was smaller in community-dwelling elderly persons or postmenopausal women than institutionalized elderly persons. There was no risk reduction among community-dwelling women with history of fracture (RR 1.02; 95% CI 0.89-1.16). Meta-regression analysis did not show differential effects depending on the daily dose of vitamin D or the baseline 25-(OH)D concentration. The evidence was not robust event to draw conclusions about the benefits or harms of vitamin D supplementation for cancer prevention.

**Randomized Controlled Trials**

1. A 2014 fair quality double-blind, placebo-controlled, RCT (n=561) compared either 2000 IU/d of alpha tocopherol (Vitamin E), 20 mg/d of memantine, the combination, or placebo in 613 patients with mild to moderate Alzheimer’s disease (AD) at 14 Veterans Affairs medical centers. The objective was to determine if they slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor. The primary outcome for the study was the Alzheimer’s disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory, designed to assess functional abilities to perform activities of daily living. There is no definitive minimally clinically important difference for the ADCS-ADL, which makes it hard to interpret the clinical significance. Results demonstrated that, over the mean follow-up time of 2.27 years, participants receiving alpha tocopherol had significantly slower decline than those receiving placebo as measured by the ADCS-ADL Inventory (LS mean change from baseline was 3.15 units less than the decline in the placebo group; p=0.03). This translates into a delay in progression in the alpha tocopherol group of 6.2 months (95% CI 5.4-7.4) compared with the placebo group. There was no statistically significant difference in change from baseline between the placebo group and the memantine and alpha tocopherol combination group or between placebo and memantine. The treatment effect was larger in the more severe group of participants. There were no significant differences between treatment groups on total adverse events or serious adverse events. There was no significant difference in mortality between alpha tocopherol (7.3%; HR 0.87; 95% CI 0.67-1.13), memantine (11.3%; HR 1.06; 95% CI 0.91-1.24), alpha tocopherol plus memantine (9.0%; HR 0.94; 95% CI 0.57-1.54) and placebo (9.4%), respectively. Overall attrition rates were high, although similar between groups.

2. A large, fair-quality, randomized, double-blind, placebo-controlled trial evaluated whether long-term MVI supplementation decreases the risk of total and site-specific cancer events among male physicians. Men were randomized and stratified by age, prior cancer, prior CV disease, and original beta carotene treatment assignment. The primary end points were total cancer and major CV events, which were measured using the intention-to-treat principle (n=14,641). Overall, 9.0% had a baseline history of cancer and 5.1% with a baseline history of CV disease. Participants were followed up for a mean of 11.2 years. Adherence at 4 years was 76.8% for the MVI group and 77.1% for placebo (p=0.71); at 8 years, adherence was 72.3% and 70.7%, respectively
(p=0.15); and at the end of follow-up, adherence was 67.5% and 67.1%, respectively (p=0.70). Overall, the rates of total cancer were 17.0 and 18.3 per 1000 person-years in the MVI and placebo groups, respectively. Men taking MVIs had a modest reduction in total cancer incidence (HR 0.92; 95% CI 0.86-0.998; p=0.04). There was no effect of a MVI on prostate cancer (HR 0.98; 95% CI 0.88-1.09; p=0.76). Total mortality was not significantly reduced (HR 0.94; 95% CI 0.88-1.02; p=0.13) and neither was cancer mortality. Based on prespecified hypothesis, daily MVI use was associated with a reduction in total cancer among the 1312 men with a baseline history of cancer (HR 0.73; 95% CI 0.56-0.96; p=0.02), but this result did not significantly differ from that observed among 13,329 men initially without cancer.

3. A very recent fair-quality double-blind, placebo-controlled RCT evaluated whether high-dose multivitamins are effective for the secondary prevention of CV events (n=17.8). Patients at least 50 years of age who had a sustained myocardial infarction at least 6 weeks before were randomly assigned to receive oral vitamins and IV chelation infusions, oral placebo and IV chelation infusions, oral vitamins and placebo IV infusions, and oral placebo and placebo IV infusions. The primary end point was a composite of time to death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. Only 18% of the subjects were women and baseline characteristics were similar between groups. Overall treatment adherence was poor; a total of 46% of patients discontinued their regimen during the study (46% in the placebo group and 46% in the vitamin groups). The most common reason for discontinuation was declining to continue taking the vitamins or placebo. Patients received treatment for a median of 31 months. A total of 76% of subjects completed at least 1 year of oral therapy and 48% completed 3 years. Women were more likely to discontinue than men. There was no difference in the primary outcome between the vitamin group and placebo group (27% vs. 30%; HR 0.89; 95% CI 0.75-1.07; p=0.21). There were no significant differences in any of the individual outcomes (death, MI, stroke, hospitalization for angina) and no significant difference in CV death. However, the results for the individual outcomes were very imprecise due to few events for each component. Serious adverse events were similar between groups (15% in the vitamin group vs. 12% in placebo).
References:


Class Update: Inhaled products for Cystic Fibrosis

Month/Year of Review: March 2014
Date of Last Review: August 2012
PDL Classes: Inhaled Antibiotics
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: DORNASE ALFA, SODIUM CHLORIDE FOR INHALATION, TOBRAMYCIN IN 0.225% NACL
- Non-Preferred Agents: AZTREONAM (CAYSTON®)

PA Criteria: A quantity limit of 56 vials/56 days and 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy) is in place for inhaled tobramycin solution (TIS) and aztreonam lysine for inhalation (AZLI), respectively.

Previous Conclusions:
- There is insufficient long-term evidence available for all drugs in the class. The longest study for tobramycin inhalation solution (TIS) is 33 months. There is no evidence for aztreonam lysine for inhalation (AZLI) beyond a 28-day course.
- Efficacy and safety has not been established for use of AZLI in patients <7 years old or TIS < 6 years old
- There is insufficient comparative evidence for efficacy and safety of TIS and AZLI.
- There is moderate quality evidence that overall, the frequencies of pulmonary exacerbations, hospitalizations, and parenteral antipseudomonal antibiotic use are improved with chronic suppressive therapy with TIS in patients with mild to severe Cystic Fibrosis (CF).
- There is low to moderate quality short term evidence that AZLI modestly improves lung function as measured by FEV1, improves patient-reported respiratory symptoms, and lengthens the time to use of additional antipseudomonal antibiotics compared to placebo.
- A Cochrane review showed demonstrated low quality evidence that inhaled antibiotics improved lung function in patients with CF and that TIS, specifically, significantly decreased hospitalization among patients.
- AZLI and TIS were well tolerated throughout all clinical trials, with cough being the most frequently reported adverse event. There have been post-marketing reports of hearing loss in patients using TIS.
- There is moderate quality evidence that treatment with hypertonic saline for patients six years of age and older improves short term lung function, decreases pulmonary exacerbations, and has a small effect on improvement in quality of life. There is insufficient evidence to determine the long term effects of hypertonic saline on mortality in patients with CF.
Conclusions:
- There is moderate quality evidence that both inhaled tobramycin and inhaled aztreonam improve lung function and quality of life in moderate to severe disease for individuals with CF and Pseudomonas (P.) aeruginosa persistently present in cultures of the airways. However, there is evidence that inhaled tobramycin reduces exacerbations in patients with CF, while the trials of inhaled aztreonam are short term with limited follow up.
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- There is insufficient evidence to recommend oral anti-psuedomonal antibiotics for pulmonary exacerbations or long-term treatment of chronic infection.
- There is low quality evidence that Tobi Podhaler is noninferior to tobramycin inhalation nebulizer solution in improving lung function.
- There is low quality evidence that Tobi Podhaler results in a higher incidence of discontinuations due to adverse events (14% vs. 8%) and total discontinuations (26.9% vs. 18.2%) than tobramycin nebulizer, respectively.

Recommendations:
- There is no new clinical evidence of effectiveness or safety resulting in recommended changes to current PDL agents. Maintain tobramycin inhalation solution as preferred and evaluate costs in executive session.
- Make tobramycin inhalation powder (Tobi Podhaler) non-preferred and consider requiring step therapy with tobramycin inhalation solution before approval.

Methods:
A Medline OVID search was conducted with the following search terms: inhaled antibiotics, tobramycin, aztreonam, cystic fibrosis, respiratory tract infections, pneumonia, Pseudomonas aeruginosa, pneumonia, bacterial infections. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to December week three 2013. The Cochrane Collection, Agency for Healthcare Research and Quality (AHRQ) National Institute for Health and Care Excellence (NICE), Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

Background:
CF is an inherited chronic disease that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues. Transport of chloride, sodium, and bicarbonate are disrupted, which may lead to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to an increased slat content in sweat gland secretions. Pulmonary disease is the leading cause of morbidity and mortality in patients with CF.

Bacterial colonization of the airway secretions may occur in patients, with P. aeruginosa as the most common pathogen in CF patients. Chronic colonization may cause respiratory insufficiency and eventual respiratory failure. Therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes. The CF foundation defined clinically meaningful endpoints as time to need additional antipseudomonal antibiotics and hospitalization. The Cystic Fibrosis Questionnaire-Revised (CFQR) has been validated as a subjective measure to assess multiple domains of patient quality of life and is approved by the FDA as a patient reported outcome measure. The clinical importance is uncertain due to no known correlation to other clinically meaningful endpoints.
There are two inhaled antibiotic agents approved for the management of patients with CF that is complicated by *P. aeruginosa*, TIS and AZLI. Both are administered for 28 days, followed by 28 days off therapy. Dornase alfa (DA) is a purified solution of recombinant human deoxyribonuclease (rhDNase), an enzyme that assists in the breakdown of DNA which accumulated in CF patients. The CF guidelines recommend the use of DA in patients with asymptomatic, mild, moderate, or severe lung disease to improve lung function and reduce exacerbation. Hypertonic saline (HS) inhalation increases hydration of airways surface liquid in patients with CF, which helps improve mucociliary clearance. For patients 6 years of age and older with CF, the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).

**New Systematic Reviews:**
A Cochrane Collaboration systematic review evaluated the benefit or harm of oral anti-psuedomonal antibiotic therapy for people with CF, colonized with *P. aeruginosa*, in the treatment of pulmonary exacerbation and long-term treatment of chronic infection. Five randomized, open-label trials were identified in the literature search, all of them comparing oral to IV interventions. Three evaluated pulmonary exacerbations and two examined long-term therapy. There was no statistically significant difference between oral antibiotics and other treatments for quality of life or lung function for either pulmonary exacerbations or long-term treatment. One trial resulted in significantly better lung function when treating an exacerbation with oral ciprofloxacin compared to IV treatment. None of the trials were blinded, increasing the risk of bias. The authors concluded that there was no conclusive evidence that an oral anti-psuedomonal antibiotic regimen is more or less effective than an alternative treatment for either pulmonary exacerbations or long-term treatment of chronic infection.

Another Cochrane systematic review attempted to determine if treatment of pulmonary exacerbations with inhaled antibiotics improves their quality of life, reduces time off school or work and improves their long-term survival. Randomized controlled trials comparing inhaled antibiotics to placebo or another inhaled antibiotic were included. Six trials (n=208) were included in the analysis. However, risk of bias was difficult to assess as results were not fully reported and only limited data was available. The lack of evidence made it difficult to demonstrate whether one treatment was superior to the other or not. The authors concluded that further research is needed to establish whether inhaled tobramycin may be used as an alterative to intravenous tobramycin for some pulmonary exacerbations.

Littlewood et al performed a network meta-analysis on inhaled antibiotics used in cystic fibrosis patients to treat *P. aeruginosa* lung infections. Seven trials (n=1798) were included that used at least one of the following medications: tobramycin, colistimethate, or aztreonam. The primary outcome studied was percent change in forced expiratory volume in one second (FEV₁) from baseline after four weeks. Tobramycin inhalation powder showed improvement in percent of FEV₁ from baseline compared with aztreonam (3.64%; 95% CI -1.04 to 8.26) and colistimethate (5.77%; 95% CI -1.20 to 12.75), although the difference was not statistically significant. There was no difference in percent of FEV₁ between tobramycin powder and tobramycin nebulizer formulations (-0.55%; 95% CI -3.50 to 2.4). Tobramycin nebulizer solution patients had significantly improved percent of FEV₁ compared with aztreonam (Az vs. Tobi -4.19%; 95% CI -8.14 to -0.21) and colistimethate (Co vs. Tobi -6.32%; 95% CI -12.61 to -0.02). Conclusions should be made with caution, as outcomes discussed as endpoints were not reported in the final publication. Individual studies were not evaluated for quality.

**Guidelines:**
1) The Cystic fibrosis (CF) Foundation’s Pulmonary Clinical Practice Guidelines Committee updated their guideline for Chronic Medications for Maintenance of Lung Health in 2012. Recommendations were graded on the overall strength of the evidence and measured on the certainty of the magnitude of benefit minus
harm. All recommendations were given the grade of A, B, C, D, or I. Recommendations were also rated on the quality of the evidence used for the recommendation. High quality recommendations were based on consistent results from well-designed, well-conducted studies; conclusions were unlikely to be affected by the results of future studies. Moderate quality recommendations were considered sufficient to predict the effects of an outcome but confidence in the estimate was constrained by quality of individual studies. Low quality recommendations were based on limited, inconsistent, or flawed studies; the available evidence was considered insufficient to predict or assess a therapy outcome.  

- For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations. (Recommendation grade A, evidence level high)

- For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. (Recommendation grade B, evidence level moderate)

- For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations. (Recommendation grade I, evidence level low)

- For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life. (Recommendation grade A, evidence level high)

- For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life. (Recommendation grade B, evidence level moderate)

2) In March, 2013, the National Institute for Health and Care Excellence (NICE) issued guidance for the use of colistimethate and tobramycin dry powders for inhalation for treating pseudomonas lung infection in CF. The following were recommended:

- Tobramycin dry powder for inhalation is recommended as an option for treating chronic pulmonary infection caused by *P. aeruginosa* in people with CF only if:
  - Nebulized tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response
- Colistimethate sodium is recommended as an option only if:
  - They would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulized form and thus tobramycin therapy would other be considered

**New drugs:**
None

Author: M. Herink, Pharm.D.
New Formulations/Indications:
Tobramycin inhalation powder (Tobi Podhaler) was approved by the FDA in March of 2013 for management of Cystic fibrosis with *P. aeruginosa* infections. It is formulated into capsules for inhalation using the Podhaler device. This is different than tobramycin inhalation solution, which is formulated into an ampule for inhalation using a nebulizer.

Approval was based on two placebo randomized controlled trials and one active-comparator open-label randomized trial. The placebo-controlled trials included patients between 6 and 21 years old with an FEV₁ of 25% to 80% of predicted normal values. The first placebo-controlled trial was stopped early for demonstrated benefit, with a relative change in FEV₁ to end of cycle 1 dosing of 12.54% in the tobramycin group compared to 0.09% in the placebo group (p=0.002). Respiratory-related hospitalizations occurred in 4.4% of patients in the tobramycin group compared to 12.2% in the placebo group. The second placebo-controlled trial did not show a significant difference in change in FEV₁ between tobramycin inhalation powder and placebo (8.19% vs. 2.27%; p=0.157). The authors noted that this study was underpowered due to barriers in recruiting patients.

Konstan et al was a randomized, poor-quality, open-label trial, comparing two formulations of inhaled tobramycin for treating *P. aeruginosa* infections in CF patients over six years old. This was the primary safety analysis. Subjects (n=517) were randomized in a 3:2 ratio to tobramycin inhalation powder or tobramycin nebulizer solution. The study duration was three treatment cycles of 28 days on tobramycin and 28 days off. Subjects on the tobramycin powder were more likely to experience adverse events than the nebulizer patients (90.3% vs. 84.2%; p<0.05) and experienced more discontinuations due to adverse events (14% vs. 8%, respectively). Serious adverse events were similar between groups (27.4% vs. 29.2%); three deaths occurred during the study, all in the powder group, although no deaths were related to the study medication. Change in percent of FEV₁ was similar with 1.1% relative change between groups, which was within the predefined 6% margin for noninferiority for the powder compared with the nebulizer solution. Eradication of *P. aeruginosa* at the end of treatment was similar between groups: 11.6% of the powder and 9.9% of the nebulizer subjects were *P. aeruginosa* free after treatment. Patients’ requiring an additional antibiotic during treatment for *P. aeruginosa* infection was significantly higher for the powder group than the nebulizer subjects (64.9% vs. 54.5%; p=0.0148); although the number of patients hospitalized for respiratory events was not significantly different between treatment groups (24.4% vs. 22.0%). Outcome reporting could be difficult to follow as endpoints were not always identified or described prior to reporting.

New FDA safety alerts:
None

New Trials (Appendix 1):
A total of 46 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, three relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Schuster et al conducted an open label controlled trial comparing nebulized tobramycin and inhaled colistimethate. CF patients (n=380) aged 6 years and older with a confirmed chronic *P. aeruginosa* infection were randomized to twice daily tobramycin given in alternating 28-day cycles or twice daily colistimethate given every day through the study duration of 24 weeks. The primary endpoint was change in percent of FEV₁ at study end; 261 subjects finished the study per protocol. There was no significant difference between treatment groups in change in percent of FEV₁ (-0.56%; 95% CI -2.71 to 1.70%). A secondary study
measurement was an evaluation of colistin resistant microorganisms present in subjects’ sputum. The minimum inhibitory concentration to inhibit 50% of bacterial isolates (MIC\textsubscript{50}) was similar for both treatment groups throughout the study. No statistical analysis was provided. The rate of adverse events was much higher in the colistimethate group than in the tobramycin subjects (82.2% vs. 46.6%). This was also true for percent of patients discontinuing due to adverse events (9.7% vs. 1.6%). This was a low quality study. Clinically relevant outcomes such as \textit{P. aeruginosa} eradication or decreased hospitalizations were not studied. No details were provided for randomization protocol or other study methodology, and the study was open label.\textsuperscript{11}

Proesmans et al compared a 28 day regimen of tobramycin inhalation solution with three months of inhaled Na colistimethate plus oral ciprofloxacin. Children (n=58) under 18 years old with CF and a new \textit{P. aeruginosa} infection were randomized to one of the two treatment groups and followed for two years. The primary outcome was \textit{P. aeruginosa} eradication at the end of treatment. Secondary outcomes were time to relapse, change in FEV\textsubscript{1}, body mass index (BMI) and \textit{P. aeruginosa} status at two years. There was no difference in the rate of \textit{P. aeruginosa} elimination between treatment groups at the end of therapy (89.7% vs. 79.3%; RR 0.88, 95% CI 0.71 to 1.11). The median time to relapse of \textit{P. aeruginosa} infection was nine months for colistimethate (95% CI 0.0 to 19.0 months) and five months for tobramycin (95% CI 1.7 to 8.3 months) although this was not a significant difference (p=0.608). After two years, 19 colistimethate and 13 tobramycin patients remained \textit{P. aeruginosa} free (p=0.78). No difference was seen in change in FEV\textsubscript{1} or BMI between treatment groups. This was a fair quality open-label study that had well described methodology for randomization, outcome procedures, and follow-up.\textsuperscript{12}

Taccetti et al evaluated inhaled tobramycin versus inhaled colistin in Cystic fibrosis patients with a new \textit{P. aeruginosa} infection. Subjects (n=223) were randomized to treatment for a duration of 28 days in this open label study. Both treatment arms were given oral ciprofloxacin. The primary outcome was eradication of \textit{P. aeruginosa} after six months. This occurred in 62.8% of colistin and 65.2% of tobramycin patients (OR 0.90; 95% CI 0.52 to 1.55). There was a noted increase in Stenotrophomonas maltophilia infection (OR 3.97; 95% CI 2.27 to 6.94) although there was no difference between occurrence in treatment groups (p =0.88). This was a low quality study.\textsuperscript{13}
References:


Appendix 1: Abstracts of Randomized Control Trials


Purpose To assess efficacy and safety of a new dry powder formulation of inhaled colistimethate sodium in patients with cystic fibrosis (CF) aged ≥6 years with chronic Pseudomonas aeruginosa lung infection. Study design and methods A prospective, centrally randomised, phase III, open-label study in patients with stable CF aged ≥6 years with chronic P aeruginosa lung infection. Patients were randomised to Colobreathe dry powder for inhalation (CDPI, one capsule containing colistimethate sodium 1 662 500 IU, twice daily) or three 28-day cycles with twice-daily 300 mg/5 ml tobramycin inhaler solution (TIS). Study duration was 24 weeks.

Results 380 patients were randomised. After logarithmic transformation of data due to a non-normal distribution, adjusted mean difference between treatment groups (CDPI vs TIS) in change in forced expiratory volume in 1 s (FEV1% predicted) at week 24 was −0.98% (95% CI −2.74% to 0.86%) in the intention-to-treat population (n=373) and −0.56% (95% CI −2.71% to 1.70%) in the per protocol population (n=261). The proportion of colistin-resistant isolates in both groups was ≤1.1%. The number of adverse events was similar in both groups. Significantly more patients receiving CDPI rated their device as ‘very easy or easy to use’ (90.7% vs 53.9% respectively; p<0.001).

Conclusion CDPI demonstrated efficacy by virtue of non-inferiority to TIS in lung function after 24 weeks of treatment. There was no emergence of resistance of P aeruginosa to colistin. Overall, CDPI was well tolerated.


In patients with cystic fibrosis (CF), treatment of new P aeruginosa (Pa) infection postpones the occurrence of chronic infection, but the best eradication regimen is unknown. Aim of the study: Compare 2 Pa eradication regimens in children with new Pa infection.

Methods: Children with CF (0–18 years) and a new isolation of Pa from sputum, cough swab or BAL were randomized to treatment with tobramycin inhalation solution for 28 days (TIS) or inhaled sodium colistimethate (2×2 mill U/day) plus oral ciprofloxacin (30 mg/kg/day) for 3 months (CC). Airway cultures were taken for 6 consecutive months, then every 3 months. The primary outcome was Pa eradication at the end of treatment. Secondary outcome parameters were: time to Pa relapse from end of treatment, total and Pa specific IgG, FEV1, BMI and Pa status at 2 year follow-up.

Results: 58 patients with new Pa isolation were randomized. Their median age was 9 years (IQR 4.7–13.1) and their median FEV1 98% predicted (IQR 87–107). Eighteen treatments concerned the first Pa isolation ‘ever’ (TIS; B: CC: 10). For the remaining, median time since previous Pa was 19 months (IQR 9–41). Eradication at end of treatment was similar for both treatments: 26/29 CC and 23/29 in TOBI treated patients (p=0.47). Median time to recurrence of Pa was 9 months (95% CI 0.0–19.0) for CC and 5 months (95% CI 1.7–8.3) for TIS (p=0.608). After 1 year, the 2 groups did not differ in change in total and Pa specific IgG, FEV1 and BMI. After 2 years, 10% of patients had chronic Pa infection.

Conclusion: In children with CF and new Pa infection, inhalation of TIS (28 days) or CC (3 months) resulted in similar eradication success at the end of treatment (80 and 90% respectively) and similar clinical evolution during the first 2 years of follow-up.


Background Pseudomonas aeruginosa chronic pulmonary infection is an unfavourable event in cystic fibrosis. Bacterial clearance is possible with an early antibiotic treatment upon pathogen isolation. Currently, no best practice exists for early treatment. The efficacy of two different regimens against initial P aeruginosa infection was assessed.

Methods In a randomised, open-label, parallel-group study involving 13 centres, the superiority of inhaled tobramycin/oral ciprofloxacin compared with inhaled colistin/oral ciprofloxacin (reference treatment) over 28 days was evaluated. Patients were eligible if they were older than 1 year with first or new P aeruginosa isolation. Treatments were assigned equally by centralised balanced randomisation, stratified by age and forced expiratory volume in 1 s values. The participants and those giving the intervention were not masked to arm assignments. The primary endpoint was P aeruginosa eradication, defined as three successive negative cultures in 6 months. Analysis was by intention to treat.

Results 105 patients were assigned to inhaled colistin/ oral ciprofloxacin (arm A) and 118 to inhaled tobramycin/ oral ciprofloxacin (arm B). All patients were analysed. P aeruginosa was eradicated in 66 (62.8%) patients in arm A and in 77 (65.2%) in arm B (OR 0.90, 95% CI 0.52 to 1.55, p=0.81). Following treatment, an increase in Stenotrophomonas maltophilia was noted (OR 3.97, 95% CI 2.72 to 6.94, p<0.001) with no differences between the two arms (OR 0.89, 95% CI 0.44 to 1.78, p=0.88).

Conclusions No superiority of treatment under study was demonstrated in comparison to the reference treatment. Early eradication treatment was associated with an increase in S maltophilia.


Author: M. Herink, Pharm.D.
Background: A light-porous-particle, dry-powder formulation of tobramycin was developed, using PulmoSphere® technology, to improve airway delivery efficiency, substantially reduce delivery time, and improve patient convenience and satisfaction. We evaluated the safety, efficacy and convenience of tobramycin inhalation powder (TIP™) versus tobramycin inhalation solution (TIS, TOBI®) for treating Pseudomonas aeruginosa infection in cystic fibrosis (CF) patients aged ≥6 years.

Methods: In this open-label study, 553 patients were randomized 3:2 to TIP (total 112 mg tobramycin) via the Novartis T-326 Inhaler or TIS 300 mg/5 mL via PARI LC® PLUS nebulizer twice daily for three treatment cycles (28 days on-drug, 28 days off-drug). Safety, efficacy, and treatment satisfaction outcomes were evaluated.

Results: TIP was generally well-tolerated; adverse events were similar in both groups. The rate of cough suspected to be study drug related was higher in TIP-treated patients (TIP: 25.3%; TIS: 4.3%), as was the overall discontinuation rate (TIP: 26.9%; TIS: 18.2%). Increases in FEV1% predicted from baseline to Day 28 of Cycle 3 were similar between groups; the mean reduction in sputum P. aeruginosa density (log10 CFU/g) on Day 28 of Cycle 3 was also comparable between groups. Administration time was significantly less for TIP (mean: 5.6 versus 19.7 min, p 0.0001). Treatment satisfaction was significantly higher for TIP for effectiveness, convenience, and global satisfaction.

Conclusions: TIP has a safety and efficacy profile comparable with TIS, and offers a far more convenient treatment option for pseudomonas lung infection in CF.
New Drug Evaluation: Delayed Release Cysteamine

Month/Year of Review: January 2014
Generic Name: delayed-release cysteamine bitartrate
PDL Class: None

End date of literature search: December 1, 2013
Brand Name (Manufacturer): Procysbi™ (Raptor Pharmaceuticals)
Dossier Received: Pending

FDA Approved Indication: Delayed-release (DR) cysteamine bitartrate is indicated for managing nephropathic cystinosis in adults and children ≥6 years of age and should be prescribed by a physician experienced with the disease’s management.

Research Questions:
- Is cysteamine DR superior or noninferior to immediate release (IR) cysteamine bitartrate (Cystagon) for preventing treatment failure, relapse, or death from nephropathic cystinosis?
- Is there evidence cysteamine DR is safer than IR for treating nephropathic cystinosis?

Conclusions:
- At this time, the evidence supporting cysteamine DR is noninferior or superior to cysteamine IR is low, as only one phase 3, open-label crossover study in which patients received cysteamine DR for three weeks has been published.
- While the phase 3 study did demonstrate the DR formulation was noninferior to the IR formulation in depleting WBC cystine levels, the study did not address how effective cysteamine DR is in delaying complications associated with cystinosis and improving treatment adherence, quality of life, and life expectancy. The trial population also did not include patients with renal transplants, gastric tubes or proton pump inhibitor (PPIs) use.
- Although use of a surrogate endpoint and small patient numbers were shortcomings, cystinosis is a rare disease, which limits the subject pool. Also, the surrogate endpoint, depletion of cystine, has been associated with improved outcomes for patients with cystinosis.
- The greater incidence of adverse reactions, particularly gastrointestinal disorders, among patients taking cysteamine DR may offset the improvement in adherence one would expect from switching from every 6 hour dosing to every 12 hour dosing. In the phase 3 crossover study, 79% of patients taking cysteamine DR experienced treatment-related adverse reactions compared with 22% of cysteamine IR patients (NNH 2). This was primarily due to gastrointestinal adverse reactions (NNH 3). Despite the high number of patients experiencing an ADR, no patients discontinued the medication and only 1 patient experienced a serious ADR while taking the DR formulation compared with none while taking the IR formulation. As these observations were made over a 3 week period, long-term tolerance and adverse reaction profile for the DR formulation remain uncertain.
Cysteamine is the only treatment for cystinosis, a disease that results in severe complications and mortality at an early age without constant and lifelong treatment. The DR formulation has twice daily dosing, as opposed to every 6 hour dosing; therefore, patients could sleep through the night.

Recommendations:
- Prior authorize cysteamine DR to limit its use to patients with documentation of nephropathic cystinosis and intolerance or nonadherence to cysteamine IR or inability to achieve a WBC cystine level <1 nmol ½ cystine per mg protein, preferably from a physician experienced in managing nephropathic cystinosis

Reason for Review:
Cysteamine DR, is a recently approved formulation of cysteamine bitartrate, the only treatment for nephropathic cystinosis. It costs approximately 1000 times more than the currently available immediate release formulation. This review will evaluate the evidence for the efficacy and safety of cysteamine DR.

Background:
Until the introduction of cysteamine DR, cysteamine IR (Cystagon) has been the only available FDA-approved cystine-depleting agent for treating cystinosis. Cysteamine IR’s side effects and strict every six-hour dosing, which requires nightly awakening, negatively affect the quality of life for the estimated 500 U.S. patients who have cystinosis and their families. About 70 to 80% of cystinosis patients are non-adherent to the cysteamine IR regimen and nearly 8% of patients will not take the drug. About 69% of those who will not take cysteamine IR cite side effects and intolerance as the reason. In a Dutch study of cystinosis, only 23% of patients adhered to strict every 6 hour dosing. Failure to adhere to the cysteamine IR regimen results in more rapid disease progression.

Cystinosis is a rare autosomal recessive disorder that results in early death even when treated. A defect in cystinosin, a lysosomal transmembrane protein that transports cystine to the cytoplasm where it is reduced to cysteine, leads to cystine accumulation in all organs and tissues. Normal persons and cystinosis heterozygotes have WBC cystine levels <0.2 and usually <1 nmol ½ cystine per mg protein, respectively, while untreated nephropathic cystinosis patients have WBC cystine levels >2 nmol ½ cystine per mg protein.

Cystinosis has been classified into three types:
1. Nephrotic or classic infantile cystinosis. When left untreated, this form is associated with proximal tubular Fanconi syndrome at 6 to 12 months of age, glomerular failure in the first decade of life, and various nonrenal complications, including photophobia, linear growth failure, and delayed puberty and hypogonadism in males. Over time, major complications develop, including blindness, progressive distal vacuolar myopathy, extraparenchymal restrictive lung disease, renal osteodystrophy, skeletal abnormalities, swallowing dysfunction, hepatomegaly, inflammatory bowel disease, insulin-dependent diabetes, cardiomyopathy, vascular calcifications, and neurobehavioral abnormalities.
2. Intermediate. This form of cystinosis has all of the manifestations of nephritic cystinosis but does not appear until adolescence.
3. Non-nephropathic or ocular cystinosis. This form is characterized by accumulation of cystine crystals in the cornea and photophobia.
Although the FDA approved cysteamine in 1994, physicians have used the drug since 1976 to treat cystinosis.\textsuperscript{2,6} Cysteamine’s ability to deplete cystine slows the deterioration of renal function and occurrence of extrarenal complications and improves growth.\textsuperscript{6,7} However, cysteamine therapy has been burdensome. The cysteamine IR formulation is given in four divided doses, including during usual sleeping hours, with the goal of maintaining a WBC cystine level <1 nmol ½ cystine per mg protein 5 to 6 hours following the drug’s administration. WBC cystine levels are used to evaluate treatment efficacy and appropriate dosage.\textsuperscript{6,8}

Treatments for complications due to cystinosis add to the treatment burden. These include replacement of renal losses, nutritional support, full access to water, and supplementation with citrate, bicarbonate, acetate, potassium, phosphate, and vitamin D. Growth hormone for children, thyroid hormone replacement, and ACE inhibitors may be required. Furthermore, administration of some medications, such as cysteamine, by gastric tube is needed when feeding difficulties are present.\textsuperscript{6}

Although cysteamine depletes cystinotic cells of >90% of their cystine content, the drug does not cure the disease but delays its progression and improves life expectancy. Even with early cysteamine therapy and good compliance, cysteamine accumulation continues and major complications often develop.\textsuperscript{2} However, nearly every patient who does not receive early, diligent, long-term cysteamine therapy suffers a major complication by the age of 30. Therefore, cysteamine should be initiated as early as possible and maintained throughout life.\textsuperscript{3,6}

**Clinical Efficacy:**

As of the writing of this review, the FDA has not published documentation regarding the approval of cysteamine DR. However, one trial has been published.

Langman et al (2012) performed an open-label, randomized, controlled, crossover, noninferiority trial comparing the DR formulation of cysteamine (Procysbi) with the IR formulation (Cystagon). The primary endpoint was the comparison between cysteamine DR vs cysteamine IR peak WBC cystine levels measured every morning over three consecutive days at the end of each three-week treatment crossover study period. The noninferiority margin was 0.3 nmol ½ cystine per mg protein.

The trial included 43 patients at three U.S. and five European Union study centers who were randomized to cysteamine DR or cysteamine IR for 6 weeks, crossing over at 3 weeks. Included were adults and children who were able to swallow cysteamine IR intact and take a stable dose of cysteamine IR sufficient to maintain a WBC cystine level ≤2 nmol ½ cystine per mg protein and have their own kidneys, with a GFR >30 mL/min per 1.73 m\textsuperscript{2} BSA. Patients could continue all concomitant medications unchanged during both crossover periods, except for proton pump inhibitors (PPIs). Patients needed to discontinue PPIs while taking cysteamine DR but could restart them if needed.

Enrolled in the study were one adult (age >21), 15 adolescents (age 12 to 21), and 27 children (age 2-12) who together had an average daily cysteamine IR dose of 1849±536 mg/d (55.8±15.2 mg/kg/d) and average WBC cysteine level of 0.66±0.34 nmol ½ cystine per mg protein. Fifty-six percent of subjects were male, and 86% of subjects had a WBC cystine <1 nmol ½ cystine per mg protein.

After a two-week run-in period, during which cysteamine trough concentration and peak WBC cystine level were measured for three consecutive days, subjects were allocated to continue their usual every 6 hour daily cysteamine IR dose or to switch to an every 12 hour cysteamine DR dose equal to 70%
of their usual cysteamine IR dose. The researchers measured trough cysteamine concentrations and peak WBC cystine levels for three consecutive days at the beginning of each crossover period. The cysteamine DR dose could be increased once by 20 to 25% when the WBC cystine level was greater than the mean WBC cystine level during the run-in period or the previous crossover period under cysteamine IR.

Cysteamine DR was superior to cysteamine IR in the modified intent to treat (mITT) population and non-inferior in the per-protocol (PP) population. The mean peak WBC cystine levels (least-squares mean ± SEM) measured in the mITT population (n=41) were 0.97±0.19 nmol ½ cystine per mg protein for patients treated with cysteamine IR and 0.70±0.19 nmol ½ cystine per mg protein in the patients treated with cysteamine DR, for a mean difference of -0.27±0.36 (98.5% CI: -0.63 to 0.09, p<0.001). The upper end of the CI was lower than the 0.3 noninferiority limit. The mean peak WBC cystine levels measured in the PP population of patients (n=38) treated with cysteamine IR was 0.54±0.05 nmol ½ cystine per mg protein and 0.62±0.05 nmol ½ cystine per mg protein for patients treated with cysteamine DR, for a mean difference of 0.08 nmol ½ cystine per mg protein (95.8% CI: 0.00 to 0.16, p<0.0001). The PP population excluded three subjects who had a 3-day average WBC cystine level >2 nmol ½ cystine/mg protein during one of the periods under cysteamine IR and so were not considered well-controlled under cysteamine IR.

Unanswered questions include the following:
How effective is cysteamine DR
  • in delaying complications associated with cystinosis and improving treatment adherence, quality of life, and life expectancy?
  • in a population with renal transplant or gastric tubes?
  • in patients taking PPIs?
  • over the lifetime of cystinotic patients?

Clinical Safety:

Data on ADRs are based on 246 children with cystinosis receiving cysteamine or phosphocysteamine in three clinical trials, 40 healthy volunteers receiving cysteamine DR in three clinical trials, and 72 patients with nephropathic cystinosis receiving cysteamine DR in three clinical trials. In children, the most common reactions (>5% of subjects) were vomiting (35%), anorexia (31%), fever (22%), diarrhea (16%), lethargy (11%), and rash (7%). The most common reactions in healthy volunteers were diarrhea and nausea, abdominal pain/discomfort, headache, vomiting, and abnormal urine odor and in patients with nephropathic cystinosis were vomiting, abdominal pain/discomfort, headache, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash. Anaphylaxis and allergic reaction also were reported during clinical trials.

No unexpected SAEs were reported in clinical trials attributable to cysteamine DR. However, in the pivotal clinical trial for cysteamine DR, a greater incidence of adverse reactions was reported in patients on cysteamine DR compared with those on cysteamine IR. The adverse reactions that occurred in >5% of patients and in a greater percentage of patients while they were taking cysteamine IR than cysteamine DR were vomiting/emesis (19% vs 12%, respectively), nausea (16% vs 7%), abdominal pain/discomfort (14% vs 0%), headache (5% vs 0%) and dizziness (5% vs 0%). A greater percentage of patients experienced anorexia/loss of appetite while taking cysteamine IR (5%) than while taking cysteamine DR (2%).

In the extension study to the pivotal clinical trial, the most common adverse reactions among 43 patients treated 12 to 19 months were vomiting, abdominal pain, nausea, breath odor, diarrhea, and decreased appetite. After one year of cysteamine DR treatment, the average number of gastrointestinal adverse events per subject per month slightly declined (from 0.11 to 0.09) as well as the average number of total AEs/subject/month (from 0.15 to 0.08).
Adverse reactions identified post-approval of cysteamine IR include benign intracranial hypertension (or PTC) with papilledema, skin lesions, molluscoid pseudotumors, skin striae, skin fragility, joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture, and scoliosis.

*Unanswered safety questions include the following:*  
What is the ADR profile of cysteamine DR with long-term use? How will the high incidence of gastrointestinal disorders with cysteamine DR use affect adherence?
### COMPARATIVE CLINICAL EFFICACY

#### Relevant Endpoints:
1. Life expectancy
2. Time to major complications
3. Adherence
4. WBC cystine level
5. Quality of life
6. Serious adverse reactions

<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Outcomes/ Efficacy Results (98.5% CI, p-values)</th>
<th>ARR/NNT</th>
<th>Safety Results (CI, p-values)</th>
<th>ARR/NNH</th>
<th>Quality Rating; Internal Validity Risk of Bias/External Validity Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Langman (2012)</td>
<td>Cysteamine 1. DR: 70% of usual pre-study IR dose with option to increase the dose 20-25% 2. IR: Usual pre-study Q6H dose</td>
<td>Demographics (ITT): Age (mean): 11.7±4.2 Male (%): 56 Age 2-12 (no.): 27 Age 12-21 (no.): 1 Age &gt;21 (no.): 1 Daily IR dose: 1849±536 mg/d (55.8±15.2 mg/kg) WBC cystine (nmol ½ cystine/mg protein): 0.66±0.34 WBC cystine &lt;1 nmol ½ cystine/mg protein (%): 86</td>
<td>mITT 41</td>
<td>WBC cystine level (nmol ½ cystine/mg protein): 1. DR: 0.70±0.19 2. IR: 0.97±0.19 Difference: -0.27±0.36 (98.5% CI: -0.63 to 0.09, p&lt;0.001)</td>
<td>Treatment-related AEs: DR: 79% IR: 22% Treatment-related gastrointestinal disorders: DR: 55.8% IR: 19.5% Treatment-related SAEs: DR: 0.02% IR: 0% Treatment-related AEs leading to D/C of study drug: DR: 0% IR: 0%</td>
<td>Treatment-related AEs: Treatment-related gastrointestinal disorders: Treatment-related SAEs: Treatment-related AEs leading to D/C of study drug:</td>
<td>NA</td>
<td>Quality rating: Poor Internal Validity: Selection: Randomized; allocated centrally, small patient numbers Performance: Lack of Blinding; open-label, not placebo-controlled Detection: Lack of Blinding; open-label Attrition: Low overall attrition; ITT analysis done</td>
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</table>

#### Primary Study Endpoint:
1) Peak WBC cystine levels measured every morning over three consecutive days at the end of each three-week treatment crossover study period. The noninferiority margin was 0.3 nmol ½ cystine per mg protein.

AEs: adverse events, D/C: discontinuation, DR: cysteamine delayed release, IR: cysteamine immediate release, mITT: modified intent to treat, NA: not applicable, MC: multicenter, RCT: randomized controlled trial, SAE: serious adverse event

Author: Sherri Willard-Argyres, Pharm.D.
REFERENCES
Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Cysteamine bitartrate is an aminothiol that penetrates cell lysosomes and participates in a thiol-disulfide interchange reaction that converts cystine into cysteine and cysteine-cysteamine mixed disulfide. Both molecules can exit the lysosome through those disulfide transporters that function in patients with cystinosis.

PHARMACOKINETICS

in patients with nephropathic cystinosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Bioavailability</td>
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</tr>
<tr>
<td>Protein Binding</td>
<td>52%</td>
</tr>
<tr>
<td>Elimination</td>
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</tr>
<tr>
<td>Half-Life</td>
<td>254 minutes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>not available</td>
</tr>
</tbody>
</table>

DOSE & AVAILABILITY

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>ROUTE</th>
<th>FREQUENCY</th>
<th>DOSAGE:</th>
<th>RENAL ADJ</th>
<th>HEPATIC ADJ</th>
<th>Pediatric Dose</th>
<th>Elderly Dose</th>
<th>OTHER DOsing CONSIDERATIONS</th>
</tr>
</thead>
</table>
| 25 mg or 75 mg DR capsule | oral  | Two divided doses daily | Cysteamine bitartrate-naive patients: 1/6 to 1/4 of the maintenance dose; then, raised gradually over 4 to 6 weeks. Recommended maintenance dose: 1.3 gram/m²/day, in two divided doses given every 12 hours. The | No information specific to this population provided in prescribing information | No information specific to this population provided in prescribing information | Should be used upon diagnosis of nephropathic cystinosis in children >6 years. Risks and benefits of cysteamine in patients <6 years old not established | No information specific to this population provided in prescribing information | • Should be swallowed whole or opened and sprinkled on applesauce or berry jelly, or mixed in apple or orange juice  
  • If possible, do not eat at least 2 hours before or 30 minutes after taking  
  • Titrate dose based on WBC cystine or, if unavailable, plasma cysteamine level. Measure monthly for 3 months, then quarterly for 1 year, then twice yearly minimum for patients never before treated with cysteamine IR. Measure every two weeks, then quarterly for 6 months, then twice yearly minimum for patients switching from IR to DR. In well-controlled, adherent patients plasma cysteamine is >0.1 mg/L and WBC cysteine is <1.0 nmol ½ cystine/mg protein.  
  • Adjust dose by 10% when adjustments are
dose can be increased up to 1.95 grams/m\(^2\)/day if the WBC cystine level remains higher than the target WBC cystine level and/or the target cysteamine concentration has not been achieved. See chart below.

<table>
<thead>
<tr>
<th>Weight in Pounds</th>
<th>mg of PROCYSBI Every 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>200</td>
</tr>
<tr>
<td>11-20</td>
<td>300</td>
</tr>
<tr>
<td>21-30</td>
<td>400</td>
</tr>
<tr>
<td>31-40</td>
<td>500</td>
</tr>
<tr>
<td>41-50</td>
<td>600</td>
</tr>
<tr>
<td>51-70</td>
<td>700</td>
</tr>
<tr>
<td>71-90</td>
<td>800</td>
</tr>
<tr>
<td>91-110</td>
<td>900</td>
</tr>
<tr>
<td>&gt;110</td>
<td>1000</td>
</tr>
</tbody>
</table>

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):
Cysteamine is contraindicated in patients hypersensitive to penicillamine

Warnings and Precautions:
- Skin and bone lesions resembling the clinical findings of Ehlers-Danlos syndrome have been reported in patients treated with high doses of cysteamine IR. Interrupt cysteamine DR in patients who develop lesions. The drug may be restarted at lower dose and slowly increased.
- Severe skin rashes, such as TEN, have been reported in patients taking cysteamine IR. Discontinue the cysteamine DR if the symptoms occur.
- GI ulcers and bleeding have been reported with cysteamine IR. Decrease the cysteamine DR dose if the symptoms occur.
- CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been reported with cysteamine IR. Interrupt the cysteamine DR or adjust the dose if symptoms occur.
- Leukemia and elevated alkaline phosphatase levels have been associated with cysteamine.
- Benign intracranial hypertension and papilledema have been reported in patients taking cysteamine IR, but causal relationships have not been established.

**Monitoring:** Monitor patients for skin or bone lesions and for signs and symptoms of pseudotumor cerebri. Monitor blood counts and alkaline phosphatase levels.

**Drug-Drug interactions:** Cysteamine DR should not be given with bicarbonate.

**Food-Drug Interactions:** Not reported

**Allergy/Cross Reactive Substances:** Penicillamine

**Pregnancy/lactation rating:** Category C. No adequate, well-controlled studies have been performed in pregnant women. However, cysteamine bitartrate is teratogenic and fetotoxic in rats at doses about 0.2 to 0.7 times the recommended human maintenance dose based on body surface area. Therefore, during pregnancy, the drug should be used only when the benefit justifies the risk. Whether cysteamine is present in the milk of nursing humans taking the drug is unknown. However, neonatal rats nursed by mothers receiving cysteamine have decreased survival; therefore, nursing while taking cysteamine is not recommended.

**Carcinogenesis/Mutagenesis:** Cysteamine has not been tested for its carcinogenicity in long-term animal studies. The drug produced a negative Ames test and in-vitro sister chromatid exchange assay in human lymphocytes but a positive response in hamster ovarian cells in a similar assay. In rats, cysteamine had no effect on fertility and reproductivity at 0.4 times the recommended human dose based on body surface area. At 1.7 times the RHMD, the drug reduced the fertility of the adult rats and the survival of their offspring.

**Dose Index (efficacy/toxic):** Rats died from a single oral dose of cysteamine 660 mg/kg. Acute toxicity symptoms were motor activity reduction and hemorrhage in the gastrointestinal tract and kidneys. Two human cases of cysteamine IR overdose with full recovery have been reported.

**Look-alike / Sound-alike (LA/SA) Error Risk Potential:**

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexicomp</th>
<th>Clinical Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA/SA for cysteamine</td>
<td>none</td>
<td>cystadane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cysteine</td>
</tr>
<tr>
<td>LA/SA for Procysbi</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

Author: Sherri Willard-Argyres, Pharm.D.
### ADVERSE REACTIONS

**PROCYSBI™ (cysteamine bitartrate) delayed-release capsules**

**TABLE 2: Comparison of adverse reactions that occurred in 5% or more patients while receiving immediate-release cysteamine or PROCYSBI during Trial 3**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Immediate-release cysteamine (n = 41)</th>
<th>PROCYSBI (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Vomiting/emesis</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Anorexia/loss of appetite</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
**Abbreviated Class Update: Topical Antifungal Agents**

- **Month/Year of Review:** March 2014
- **PDL Class:** Dermatologic – Topical antifungal
- **New drug:** LUZU \(^\text{(luliconazole)}\) cream
- **End date of literature search:** January 2014

**Current Status of PDL Class:**
- **Preferred Agents:** MICONAZOLE CREAM, NYSTATIN CREAM/OINTMENT
- **Non Preferred Agents:** BUTENAFINE (MENTAX\(^\circledast\)), BENZOID ACID/SALICYCLIC ACID OINTMENT (BENSAL HP\(^\circledast\)), CHLOROXYLENOL, CICLOPIROX CREAM, CLOTRIMAZOLE SOLUTION/CREAM, ECNANZOLE CREAM, KETOCONAZOLE SHAMPOO/CREAM, NAFTIFINE (NAFTIN\(^\circledast\)), NYSTATIN/TRIAMCINOLONE OINTMENT/CREAM, TERBINAFINE, TOLNAFATE (TINACTIN\(^\circledast\)), OXICONAZOLE LOTION (OXISTAT\(^\circledast\)), SERTACONAZOLE (ERTACZO\(^\text{TM}\)), SULCONAZOLE CREAM (EXELDERM\(^\circledast\)), UNDECYLENIC ACID
- **PA criteria:** Prior authorization (PA) required for non-preferred agents covering only for a funded diagnosis and trial of generic formulation.

**Research Questions:**
- Is there any new relevant evidence demonstrating differences in efficacy or safety in topical antifungal drugs, suggesting recommended changes to the current PDL?
- Is luliconazole more effective and/or safer than currently available agents?
- Are there subgroups of patients where luliconazole may be more effective or safer than currently available agents?

**Conclusions:**
- There is new low quality evidence from one systematic review and indirect comparisons that there are no statistically significant differences among the antifungals in mycologic cure rate at the end of treatment in the treatment of dermatophytosis. \(^1\)
- There is low quality evidence that butenafine and terbinafine are significantly more efficacious than were clotrimazole, oxiconazole and sertaconazole in sustained cure and terbinafine is statistically superior to ciclopirox for the treatment of dermatophytosis. \(^1\)
- There is low quality evidence based on one published fair quality study that luliconazole is effective and safe for the treatment of tinea cruris and is significantly better than placebo in achieving a complete response (21.2% vs. 4.4%; \(p<0.001\)). \(^2\) There are no comparative data between luliconazole and other topical antifungal agents.
Recommendations:

- Maintain luliconazole a non-preferred topical antifungal medication on the PDL due to lack of long term clinical outcomes data and direct comparative data to suggest better tolerability or efficacy than currently available agents.
- Evaluate comparative costs in executive session of other agents.

Previous Conclusions and Recommendations

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events

Reason for Review:
Since the last review of this class in March 2013, luliconazole (LUZU®) cream was approved by the FDA for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms Trichophyton rubrum and Epidermophyton floccosum, in patients 18 years of age and older. This update will examine the new agent’s place in therapy and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Methods:
A Medline (Ovid) literature search was conducted for new randomized controlled trials (RCT’s) and controlled clinical trials comparing medications head-to-head in the treatment of topical fungal infections with all included drugs and limits for humans, English language with the following search terms: tinea unguium, tinea capitis, tinea corporis, tinea cruris, tinea pedis, lichen planus, pityriasis versicolor, Candidiasis, vulvovaginal candida, blastomycosis, Coccidioidomycosis, Cryptococcosis, mycosis, Histoplasmosis, Onychomycosis, tinea, Chromoblastomycosis, and seborrheic dermatitis. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Rotta I et. al.¹ conducted a mixed-treatment comparison meta-analysis that evaluated and compared the efficacy of topical antifungals used in dermatophytosis treatment. The outcomes evaluated were mycologic cure at the end of treatment and sustained cure. A random-effects Bayesian mixed-treatment comparisons model was applied to combine placebo-controlled RCTs and head to head RCTs. The quality of each study was assessed using the Jadad tool and only studies with a score of 3 or more were included. When looking at direct comparisons, there was a statistically significant difference between clotrimazole and terbinafine, favoring terbinafine (OR 0.24; 95% CI 0.11-0.53). When evaluating sustained cure, there were statistically significant differences between clotrimazole and naftifine (OR 0.35; 95% CI 0.14-0.7), oxiconazole nitrate vs. terbinafine (OR 0.10; 95% CI 0.03-0.32), and naftifine vs. oxiconazole (OR 7.86; 95% CI 2.41-25.60), favoring allylamines in all comparisons.

Author: B Liang, Pharm.D
Date: March 2014
The pooled mixed treatment meta-analysis data of the 65 trials identified did not show any statistically significant differences among the antifungals in mycologic cure at the end of treatment. Regarding sustained cure, butenafine and terbinafine were significantly more efficacious than clotrimazole, oxiconazole and sertaconazole. Terbinafine also demonstrated statistical superiority when compared with ciclopirox, and naftifine showed better response compared with oxiconazole. When ranking each agent for efficacy, tioconazole was the therapy that had the greatest probability of being the best treatment considering the mycologic cure at the end of treatment outcome and miconazole was the second most efficient treatment. No inconsistency was detected in the network of evidence for both outcomes, sustaining the validity of the mixed-treatment comparisons results. The authors concluded because of the different costs of the antifungals, pharmacoeconomic analysis is required to identify the most efficient strategy for dermatophytosis management.

**New Guidelines:**
No new or updated guidelines were identified.

**New Safety Alerts, Indications:**
No new safety alerts or indications were found.

**New Drug Evaluation:**

*FDA approved indications:*
Luliconazole (LUZU®) was approved by the FDA for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.¹

*Potential Off-label Use:*
There were small number of patients under age of 18 were included in the clinical trials, which resulted FDA approval of in adults only. It is potentially used in pediatric population as well.

*Clinical Efficacy Data:*
Approval evidence for the efficacy of luliconazole was based on three randomized, double blind, phase III, placebo controlled, short term (1 or 2 weeks) trials.² Two studies evaluated luliconazole in the treatment of tinea pedis and one in tinea cruris. It was not studied in tinea corporis. At the time of this review, only one of these studies was published and was included as primary evidence for review of the efficacy and safety.² According to the FDA review, luliconazole resulted in complete clearance (clinical cure and mycological cure) of tinea pedis in 26% in one study and 14% in another study, compared to 2% and 3% in placebo groups, respectively.

Study MP-1000-01² is a fair quality study that compared the efficacy and safety of topical luliconazole cream 1% to placebo in patients with tinea cruris. A total of 256 male and female patients aged ≥12 years with clinically evident tinea cruris and eligible for modified intent-to-treat analysis were randomized 2:1 to receive luliconazole cream 1% (n=165) or vehicle (n=91) once daily for 7 days. Efficacy was evaluated at baseline and at days 7, 14, 21, and 28 based on mycology (potassium hydroxide, fungal culture) and clinical signs (erythema, scaling, pruritus). The primary outcome was complete clearance at day 28 (21 days post-treatment). Safety evaluations included adverse events and laboratory assessments. The results showed complete clearance was obtained in 21.2% (35/165) of patients treated with luliconazole cream 1% compared with 4.4% (4/91) treated with vehicle (P<0.001).
Clinical Safety:
During clinical trials with 1% luliconazole cream, the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the luliconazole and vehicle arms. Most adverse reactions were mild in severity. The following adverse reactions have been identified during post-marketing use of 1% luliconazole cream: contact dermatitis and cellulitis.

COMPARATIVE CLINICAL EFFICACY

Study Endpoints:
1) Clinical and mycologic cure at day 28 (21 days post-treatment)
2) Effective treatment at days 7, 14, 21, or 28

Relevant Study Endpoint:
1) Safety and tolerability in all patients
<table>
<thead>
<tr>
<th>Drug Regimens</th>
<th>Patient Population</th>
<th>N</th>
<th>Duration</th>
<th>Outcomes/ Efficacy Results (CI, p-values)</th>
<th>ARR/ NNT</th>
<th>Safety Results (CI, p-values)</th>
<th>ARR/ NNH</th>
<th>Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>L: luliconazole 1% cream once daily x 7 days P: Vehicle cream once daily x 7 days</td>
<td>Age ≥ 12 y/o Mean age: L/P: 41.1/39.1 Race (%of white): L/P: 59.4%/54.9% Fungal culture results (% of positive): L/P: 100%/100%</td>
<td>N= 256 (MITT Population) L = 165 P = 91</td>
<td>7 days treatment</td>
<td>Primary outcomes: Complete mycologic and clinical clearance : L: 21.2% P: 4.4% (p &lt; 0.001) Secondary outcomes: Clinical cure: L: 24.2% P: 6.6% (p &lt; 0.001) Mycologic cure: L: 78.2% P: 45.1% (p &lt; 0.001)</td>
<td>16.8%/6</td>
<td>Overall TEAEs: L: 11.3% P: 16.9% The most frequent TEAEs: L: Headache: 1.6% Nasopharyngitis: 1.6% Dysmenorrheal (1.0%) P: Headache: 2.5%</td>
<td>NA</td>
<td>Quality Rating: Fair Internal Validity: RoB Selection: Low bias; clear randomization and allocation concealment. Populations were similar at baseline. Performance: Low bias; blinding adequate, blinding of patients Detection: Low bias; blinding of monitors Attrition: Low attrition L/P: 0.6%/2.2% MITT analysis: No adjustment made for covariates. External Validity: Patient Characteristics: General healthy baseline status. Setting: Multi-centers study at 27 sites. Outcomes • Short term study. • Small sample size • Controlled settings • Unknown recurrence rate</td>
</tr>
</tbody>
</table>

*Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
*Results abbreviations: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat; NNH = number needed to harm, CI = confidence interval
*NNT/NNH are reported only for statistically significant results
*Quality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

New Trials:

Author: B Liang, Pharm.D Date: March 2014
A total of 279 citations resulted from initial literature search. After review of titles for inclusion, four potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (Appendix 2). These trials are briefly described in table 1:

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldust M et al, 2013</td>
<td>Sertaconazole 2% cream (N =30) vs. hydrocortisone 1% cream (N =30) twice a day for 4 weeks.</td>
<td>Patients with seborrheic dermatitis</td>
<td>Not defined - Efficacy of the treatment.</td>
<td>The highest level of satisfaction (90%) was observed 28 days after using sertaconazole and the level of satisfaction was 83.3% in hydrocortisone group. Relapse of the disease one month after stopping treatment was not observed in either group.</td>
</tr>
<tr>
<td>Goldust M et al, 2013</td>
<td>Sertaconazole 2% cream (N =30) vs. tacrolimus 3% cream (N =30) twice a day for 4 weeks.</td>
<td>Patients with seborrheic dermatitis</td>
<td>Not defined - Efficacy of the treatment.</td>
<td>The highest level of satisfaction (90%) was observed 28 days after sertaconazole use. Only 83.3% satisfaction was noted in the tacrolimus group (p = 0.006).</td>
</tr>
<tr>
<td>Goldust M et al, 2013</td>
<td>Sertaconazole 2% cream (N =64) vs. clotrimazole 1% cream (N =64) twice a day for 4 weeks.</td>
<td>Patients with seborrheic dermatitis</td>
<td>Not defined - Efficacy of the treatment.</td>
<td>The highest level of satisfaction (87.6%) was observed 28 days after sertaconazole administration and in clotrimazole group it was 50%. Relapse of the disease one month after stopping treatment was not observed in either group.</td>
</tr>
<tr>
<td>Tietz, H.-J et al, 2013</td>
<td>Bifonazole (N = 347) vs. placebo (N = 345) for 4 weeks</td>
<td>Patients mild-to-moderate onychomycosis after non-surgical nail ablation with urea paste.</td>
<td>The primary endpoint of the study was the overall cure rate comprising clinical cure and mycological cure (both microscopy and culture negative) in the target nail assessed 2 weeks.</td>
<td>Overall cure rate was superior in bifonazole-treated group (54.8% vs. 42.2% for placebo; P = 0.0024). The clinical cure rate was high in both treatment groups (86.6% bifonazole vs. 82.8% placebo), but proportion with mycological cure was higher with bifonazole treatment (64.5%) vs. placebo treatment 49.0%, (P = 0.0001).</td>
</tr>
</tbody>
</table>
References:


Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY
Luliconazole is an antifungal that belongs to the azole class. Although the exact mechanism of action against dermatophytes is unknown, luliconazole appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme’s activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol.

PHARMACOKINETICS
Luliconazole is the R enantiomer of a chiral molecule. The potential for inter-conversion between R and S enantiomers in humans has not been assessed. Information on the pharmacokinetics of luliconazole presented below refers to both R enantiomer and S enantiomer, if any, combined. Luliconazole is >99% protein bound in plasma. In a pharmacokinetic trial, 12 subjects with moderate to severe tinea pedis and 8 subjects with moderate to severe tinea cruris applied a mean daily amount of approximately 3.5 grams of LUZU Cream, 1% to the affected and surrounding areas once daily for 15 days. Plasma concentrations of luliconazole on Day 15 were measurable in all subjects and fluctuated little during the 24 hour interval. In subjects with tinea pedis, the mean ± SD of the maximum concentration (Cmax) was 0.40 ± 0.76 ng/mL after the first dose and 0.93 ± 1.23 ng/mL after the final dose. The mean time to reach Cmax (Tmax) was 16.9 ± 9.39 hours after the first dose and 5.8 ± 7.61 hours after the final dose. Exposure to luliconazole, as expressed by area under the concentration time curve (AUC0-24) was 6.88 ± 14.50 ng*hr/mL after the first dose and 18.74 ± 27.05 ng*hr/mL after the final dose. In subjects with tinea cruris, the mean ± SD Cmax was 4.91 ± 2.51 ng/mL after the first dose and 7.36 ± 2.66 ng/mL after the final dose. The mean Tmax was 21.0 ± 5.55 hours after the first dose and 6.5 ± 8.25 hours after the final dose. Exposure to luliconazole, as expressed by AUC0-24 was 85.1 ± 43.69 ng*hr/mL after the first dose and 121.74 ± 53.36 ng*hr/mL after the final dose.

DOSE & AVAILABILITY

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>FORM</th>
<th>ROUTE</th>
<th>FREQUENCY</th>
<th>RENAL ADJ</th>
<th>HEPATIC ADJ</th>
<th>Pediatric Dose</th>
<th>Elderly Dose</th>
<th>OTHER DOSING CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>cream</td>
<td>topical</td>
<td>Daily</td>
<td>NA</td>
<td>NA</td>
<td>The safety and effectiveness in pediatric patients have not been established.</td>
<td>No dose adjustment is necessary for the elderly.</td>
<td>Geriatric patients might experience greater sensitivity.</td>
</tr>
</tbody>
</table>

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for luliconazole at this time.

Warnings and Precautions: None.

Pregnancy Category: C.
Look-alike / Sound-alike (LA/SA) Error Risk Potential:
No look-alike/sound-alike drugs have been found to have error risk potential.

Adverse Reactions
During clinical trials with 1% luliconazole cream, the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the luliconazole and vehicle arms. Most adverse reactions were mild in severity. The following adverse reactions have been identified during post-marketing use of 1% luliconazole cream: contact dermatitis and cellulitis.
Appendix 2:

Systematic Review


Abstract

**Importance:** Considering that most randomized controlled trials compare antifungals with placebo instead of other antifungals, conventional meta-analysis is insufficient to define superiority between the evaluated strategies. To our knowledge, this is the first mixed-treatment comparison meta-analysis on antifungal treatments in the literature and shows all the evidence available at the time of the study.

**Objective:** To evaluate and compare the efficacy of topical antifungals used in dermatophytosis treatment, using mixed-treatment comparisons.

**Evidence Acquisition:** We performed a comprehensive search (up to July 31, 2012) for all entries in MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Literatura Latino Americana e do Caribe em Ciências da Saúde, and International Pharmaceutical Abstracts. Randomized controlled trials that compared topical antifungals with one another or with placebo in dermatophytosis treatment were selected for analysis. Methodologic quality of the trials was assessed using the Jadad scale. We excluded studies that scored less than 3 points. The outcomes evaluated were mycologic cure at the end of treatment and sustained cure. A random-effects Bayesian mixed-treatment comparisons model was applied to combine placebo-controlled and direct topical antifungals comparison trials. RESULTS Pooled data of the 65 trials identified did not show any statistically significant differences among the antifungals concerning the outcome of mycologic cure at the end of treatment. Regarding the sustained cure outcome, butenafine hydrochloride and terbinafine hydrochloride were significantly more efficacious than were clotrimazole, oxiconazole nitrate, and sertaconazole nitrate. Terbinafine also demonstrated statistical superiority when compared with ciclopirox (ciclopiroxolamine), and naftifine hydrochloride showed better response compared with oxiconazole. No inconsistency was detected in the network of evidence for both outcomes, sustaining the validity of the mixed-treatment comparisons results.

**Conclusions and relevance:** With the outcome mycologic cure at the end of treatment, there was no significant difference among the antifungals. Butenafine, naftifine, and terbinafine might be the best strategies for maintaining cured status. Because of the different costs of the antifungals, pharmacoeconomic analysis is required to identify the most efficient strategy for dermatophytosis management.
Randomized Clinical Trials


   **Abstract**

   **Objective:** Seborrheic dermatitis (SD) is commonly treated with anti-inflammatory products, including topical corticosteroids. This study was undertaken to compare the efficiency of sertaconazole 2% cream with hydrocortisone 1% cream in the treatment of SD.

   **Methods:** In this clinical trial study, 60 SD patients were studied. Thirty patients received local sertaconazole 2% cream and were recommended to use the cream twice a day for 4 weeks. In the control group, 30 patients received hydrocortisone 1% cream and were recommended to use the cream twice a day for 4 weeks. At the start of the study and also 2 and 4 weeks after first visit, the patients were examined by a dermatologist for signs of improvement and control of clinical symptoms.

   **Results:** The mean age of the patients was 32.23 ± 12.09. The highest level of satisfaction (90%) was observed 28 days after using sertaconazole and the level of satisfaction was 83.3% in hydrocortisone group. Relapse of the disease one month after stopping treatment was not observed in both groups treated with sertaconazole 2% cream and hydrocortisone 1% cream.

   **Conclusion:** Topical sertaconazole therapy is a considerable advancement in the treatment of SD with corticosteroids. The cure rate was somewhat higher in the sertaconazole group and it can be considered as the nonsteroidal alternative to topical steroid therapy for SD.


   **Abstract**

   The treatment of seborrheic dermatitis (SD) includes topical antifungal agents to eradicate Malassezia spp. corticosteroids to treat the inflammatory component of the disease, and keratolytics to remove scale and crust. The aim of this study was to compare the efficiency of sertaconazole 2% cream and tacrolimus 0.03% cream in the treatment of seborrheic dermatitis. In this clinical trial study, sixty patients suffering from SD were studied. Thirty patients received local sertaconazole 2% cream with a recommendation to use the cream twice a day for 4 weeks. In the control group, thirty patients received tacrolimus 0.03% cream twice a day for four weeks. At the time of referral, and 2 and 4 weeks after first visit, the patients were examined by a dermatologist to check the improvement of clinical symptoms. The mean ages of the sertaconazole and tacrolimus groups were 30.98 +/- 12.24 and 34.67 +/- 10.82, respectively. The highest level of satisfaction (90%) was observed 28 days after sertaconazole use. Only 83.3% satisfaction was noted in the tacrolimus group. The relationship between patient satisfaction and sertaconazole 2% cream receive in 28th day was significant (P = 0.006). Sertaconazole 2% cream may be an excellent alternative therapeutic modality for treating seborrheic dermatitis.

**Abstract**

Treatment of seborrheic dermatitis (SD) is an important issue in dermatology. This study was undertaken to compare efficiency of sertaconazole 2% cream vs. clotrimazole 1% cream for the treatment of seborrheic dermatitis. One hundred twenty eight patients suffering from SD were studied. Patients were randomly divided into two groups. Sixty four patients received local sertoconazole 2% cream and in control group 64 patients received clotrimazole 1% cream. They were recommended to use the cream twice a day for 4 weeks. At the beginning of referring and 2 and 4 weeks after first visit, the patients were examined by a dermatologist to assess improvement of clinical symptoms. The mean age of sertaconazole and clotrimazole group patients was 34.78±/13.54 and 38.68+/11.88, respectively. The highest level of satisfaction (87.6%) was observed 28 days after sertaconazole administration and in clotrimazole group it was 50%. Relapse of the disease one month after stopping treatment was not observed in groups treated with sertaconazole 2% cream and clotrimazole 1% cream. This study suggests that sertaconazole 2% cream is an effective and well-tolerated treatment for moderate to severe facial seborrheic dermatitis.


**Summary**

Onychomycosis is a common fungal infection most often affecting the toenails. If untreated, it can cause discomfort sufficient to reduce quality of life. To evaluate efficacy and safety of bifonazole cream vs. placebo in onychomycosis treatment after non-surgical nail ablation with urea paste. Fifty-one study centres randomized 692 subjects with mild-to-moderate onychomycosis to receive bifonazole 1% cream or placebo for 4 weeks following non-surgical nail ablation with urea 40% paste over 2–4 weeks. Efficacy of the two phase treatment was evaluated by overall cure of the target nail comprising clinical and mycologic cure 2 weeks, 3 and 6 months after end of treatment. At 2 weeks (primary endpoint), overall cure rate was superior in bifonazole-treated group (54.8% vs. 42.2% for placebo; \( P = 0.0024 \)). The clinical cure rate was high in both treatment groups (86.6% bifonazole vs. 82.8% placebo), but proportion with mycological cure was higher with bifonazole treatment (64.5%) vs. placebo treatment 49.0%, \( P = 0.0001 \). We observed higher early overall cure rate with 4 weeks topical bifonazole compared with placebo after removal of infected nail parts with urea. This two stage treatment was well tolerated and offers an additional option in topical onychomycosis therapy.
Month/Year of Review: March 2014
Date of Last Review: April 2012
PDL Classes: Tobacco Cessation Products
Source Document: Abbreviated Class Review: Tobacco Cessation Products

Current Status of PDL Class:
- Preferred Agents: BUPROPION HCL TABLET SR, NICOTINE PATCH DYSQ, NICOTINE PATCH TD24, NICOTINE POLACRILEX GUM, NICOTINE POLACRILEX LOZENGE, VARENICLINE TARTRATE (CHANTIX®)
- Nonpreferred Agents: NICOTINE NASAL SPRAY (NICOTROL®), NICOTINE INHALER (NICOTROL®)

Previous Recommendations:
- Add Nicotine replacement therapy (NRT) products including the patch, gum and lozenges as preferred drugs on the PDL with a quantity limit for six months of treatment.
- Due to no differences in safety or efficacy between the NRT products, evaluate comparative costs for further decisions.
- Make bupropion sustained release (generic Zyban) a preferred drug.
- Make varenicline a preferred agent on the PDL with a quantity limit for twelve weeks of treatment within 6 months.
- Require prior authorization criteria for non-preferred products, NRT beyond 6 months in the absence of behavioral counseling, and varenicline beyond 12 weeks requiring the patient has quit for a second fill of varenicline and that the patient is enrolled in a smoking cessation behavioral counseling program in addition to medication therapy.

PA Criteria: Prior authorization criteria are currently in place for nonpreferred nicotine replacement therapy. In addition, requests for greater than 12 weeks of varenicline or six months of nicotine replacement therapy require a PA (Appendix 1).

Conclusions and Recommendations:
- No further review or research needed at this time; update PA criteria.
- Evaluate comparative costs in executive session.

Methods:
A Medline OVID search was conducted with the following search terms: tobacco use disorder, tobacco use cessation, smoking, smoking cessation, tobacco abstinence, tobacco cessation products, nicotine, nicotine replacement agents, nicotine patch, nicotine gum, nicotine lozenge, nicotine inhaler, nicotine nasal spray, bupropion, varenicline, Chantix, clonidine, and nortriptyline. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to January week one 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
The Cochrane Collaboration published a systematic review and meta-analysis on smoking cessation agents to assess comparative efficacy and safety. Varenicline, bupropion and nicotine replacement therapy (NRT) agents were the primary focus although many off-label agents were included (i.e. clonidine, nortriptyline). The primary outcome measured was continuous abstinence for at least six months from the start of treatment. Comparative safety was evaluated through the incidence of serious adverse events associated with treatment. Twelve treatment-specific Cochrane reviews were included with 267 trials (n=101,804). When compared with placebo, NRT (OR 1.84; 95% CI 1.71
to 1.99; 119 studies), varenicline (OR 2.88; 95% CI 2.40 to 3.47; 15 studies) and bupropion (OR 1.82; 95% CI 1.60 to 2.06; 36 studies) patients were significantly more likely to remain tobacco free. No difference was seen between treatment with NRT (patch, gum, lozenge, spray or inhaler) or bupropion (OR 0.99; 95% CI 0.86 to 1.13; 9 studies) when compared directly for tobacco abstinence. When compared with NRT (patch, gum, lozenge, spray or inhaler), varenicline was found to be more effective (OR 1.57; 95% CI 1.29 to 1.91). Varenicline measured against single agents was more effective no matter the NRT formulation: vs. patch (OR 1.51; 95% CI 1.22 to 1.87); vs. gum (OR 1.72; 95% CI 1.38 to 2.13); or vs. ‘other’ NRT (lozenges, spray, or inhaler) (OR 1.42; 95% CI 1.13 to 1.79). Varenicline was found to be more effective than bupropion (OR 1.59; 95% CI 1.29 to 1.96; 3 studies). When compared with combination NRT, varenicline was not more effective for tobacco abstinence (OR 1.06; 95% CI 0.75 to 1.48). No single NRT treatment was significantly more effective than any other. In safety analysis, rates of serious adverse events were found to be similar between varenicline and placebo (RR 1.06; 95% CI 0.72 to 1.55; 14 trials). Rates of cardiac events were also similar between varenicline and placebo (RR 1.26; 95% CI 0.62 to 2.56); as were rates of neuropsychiatric events (RR 0.53; 95% CI 0.17 to 1.67). Compared with placebo, bupropion also showed no significant difference in cardiac events (RR 0.77; 95% CI 0.37 to 1.59) or neuropsychiatric events (RR 0.88; 95% CI 0.31 to 2.50). Seizures occurred six times in bupropion patients versus no occurrence for placebo patients; this is a rate of 0.07%. The authors conclude that varenicline, bupropion and NRT all improve the likelihood of sustained tobacco abstinence with a low risk of severe adverse events. This meta-analysis was based on several systematic reviews rated as high quality based on AMSTAR ratings. Individual trial quality was not reported within this analysis, although the authors acknowledge that quality varied considerably; 81% of varenicline trials were considered high quality, while only 21% of NRT trials were given this rating.¹

The Cochrane Collaboration updated their systematic review evaluating the efficacy of nicotine replacement treatment (NRT) for tobacco abstinence. The primary outcome was sustained quit rates after at least six months after treatment. One hundred and seventeen trials were included in the review with 51,265 trial participants. Patients on any type of NRT were more likely to remain tobacco abstinent than placebo or control subjects (RR 1.60; 95% CI 1.53 to 1.68). Individual NRT products were also all more effective than placebo for tobacco abstinence: gum (RR 1.49; 95% CI 1.40 to 1.60; 53 trials), nicotine patch (RR 1.64; 95% CI 1.52 to 1.78; 43 trials), lozenges (RR 1.95; 1.61 to 2.36; 6 trials), inhaler (RR 1.90; 95% CI 1.36 to 2.67; 4 trials), and nasal spray (RR 2.02; 95% CI 1.49 to 2.73; 4 trials). Combination treatment with the patch and a second NRT product was more effective than any NRT alone (RR 1.34; 95% CI 1.18 to 1.51; 9 trials). NRT (any type) compared with bupropion was similar in efficacy (RR 1.01; 95% CI 0.87 to 1.18; 5 trials); although combination treatment bupropion and an NRT product was more effective than bupropion alone (RR 1.24; 95% CI 1.06 to 1.45; 4 trials). Individual study quality was evaluated for randomization, allocation concealment, blinding, incomplete outcomes data and other biases. Most trials were considered fair to low quality with only 19 trials rated as having adequately reported blinding, allocation concealment and randomization methodology.²

The Cochrane Collaboration published an updated systematic review on the effectiveness of nicotine receptor partial agonists for smoking cessation. The authors included 19 trials (n= 12,223) which compared varenicline to either placebo, bupropion or nicotine replacement therapy (NRT). The primary outcome measured was continued tobacco abstinence at least six months after treatment ends. Compared with placebo, varenicline treated subjects were more likely to remain tobacco free after six months or longer post-trial end (RR 2.27; 95% CI 2.02 to 2.55; 14 trials). Four trials compared varenicline at lower than standard dosing (< 1 mg BID) with placebo. The varenicline patients were again more likely to remain tobacco abstinent than the placebo cohort (RR 1.09; 95% CI 1.02 to 1.16). Three trials had a direct comparison between varenicline and bupropion for continued tobacco abstinence measured one year after the end of treatment. Again the varenicline subjects were more likely to remain tobacco free than their counterparts in the bupropion group (RR 1.52; 95% CI 1.22 to 1.88). Comparison, however, with NRT at six months was statistically insignificant (RR 1.13; 95% CI 0.94 to 1.35; 2 trials). Secondary outcomes examined were related to the safety of varenicline. Seventeen trials measured serious adverse events which occurred either during or after the trial. Varenicline patients were found to be more likely have had a serious adverse event than their placebo or active comparator comparators (RR 1.36; 95% CI 1.04 to 1.79). The authors found little evidence in their review of any increase in psychiatric or cardiac adverse events with varenicline treatment. Individual study quality was evaluated for
randomization, allocation concealment, blinding, incomplete outcomes data and other biases. Of the 19 trials included in the varenicline analysis, 13 were judged to have provided adequate information randomization, allocation concealment and blinding and were considered to have minimal risk of bias.  

Mills et al conducted a systematic review to compare the efficacy of high dose nicotine replacement therapy (NRT) or combination NRT with standard dose NRT, varenicline or bupropion for sustained tobacco abstinence. The primary outcome was measured at four different time points: short term (< four weeks, three months, six months and twelve months; 146 randomized controlled trials were included. Trials were included if a placebo or active control was used and the analysis for all treatments employed a random-effects pairwise meta-analysis and a Bayesian multiple treatment comparison. All treatments except combination NRT were statistically superior for patients remaining tobacco abstinent for all time points when compared with placebo. Combination NRT was not significantly different than treatment with placebo for tobacco abstinence at three months (RR 1.29; 95% CI 0.73 to 2.07) and 12 months post treatment (RR 1.34; 95% CI 0.96 to 1.84). For all time points, standard dose NRT patch showed similar efficacy to both combination NRT and bupropion treatment. High dose NRT (>22 mg nicotine patch per day) was only significantly superior to standard dose NRT in the short term (RR 1.14; 95% CI 1.07 to 1.21) and six months after treatment (RR 1.32; 95% CI 1.11 to 1.57). Varenicline was more efficacious at all time points when compared with standard dose NRT (short term RR 1.43, 95% CI 1.26 to 1.60; three months RR 1.48, 95% CI 1.23 to 1.75; six months RR 1.38, 95% CI 1.15 to 1.64; and at 12 months RR 1.65, 95% CI 1.29 to 2.07). Varenicline was also more efficacious at most time points when compared with high dose NRT (short term RR 1.29, 95% CI 1.12 to 1.46; three months RR 1.40, 95% CI 1.05 to 1.80; six months RR 1.05, 95% CI 0.80 to 1.36; and 12 months RR 1.47, 95% CI 1.06 to 2.01); when compared with combination NRT (short term RR 1.28, 95% CI 1.02 to 1.53; three months RR 1.85, 95% CI 1.15 to 2.65; six months RR 1.31, 95% CI 0.95 to 1.75; and 12 months RR 1.78, 95% CI 1.25 to 2.41); and when compared with bupropion (short term RR 1.29, 95% CI 1.12 to 1.45; three months RR 1.43, 95% CI 1.24 to 1.63; six months RR 1.34, 95% CI 1.13 to 1.57; and 12 months RR 1.61, 95% CI 1.32 to 1.93). Bupropion treatment had similar efficacy to both combination and high dose NRT at all time points. Individual trial quality was not evaluated for this meta-analysis making it difficult to measure the overall strength of evidence of the conclusions.

**Guidelines:**
The American College of Chest Physicians updated their guidelines for the treatment of tobacco use in lung cancer published in CHEST in May 2013. Recommendations used are based on the GRADE Working Group classifications. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled “1”. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled “2”. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation. 

- We recommend that current smokers undergoing low-dose CT screening be provided with cessation interventions that include counseling and pharmacotherapy (Grade 1B)
- Among lung cancer patients undergoing surgery, we recommend perioperative cessation pharmacotherapy as a method for improving abstinence rates (Grade 1B)
- For lung cancer patients attempting cessation in conjunction with surgical interventions, we recommend initiating counseling and pharmacotherapy at the outset of surgical intervention (Grade 1B)
- Among lung cancer patients undergoing chemotherapy, we recommend cessation interventions that include counseling and pharmacotherapy to improve abstinence rates (Grade 1B)
- Among lung cancer patients with depressive symptoms, we suggest cessation pharmacotherapy with bupropion as a method to improve abstinence rates, depressive symptoms, and quality of life (Grade 2B)
The Global Initiative for Chronic Obstructive Lung Disease updated their guidelines for their strategy for diagnosis, management, and prevention of COPD in 2013. Recommendations were given a grade of A, B, C, or D based on the level of evidence for the recommendation. Grade A recommendations were based on evidence from endpoints of well-designed randomized control trials (RCTs) and require a substantial numbers of studies involving substantial numbers of participants. Grade B recommendations were based on evidence from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B recommendations were made when few randomized trials existed, were small in size, were undertaken in a population that differs from the target population of the recommendation, or when the results were somewhat inconsistent. Grade C recommendations were from the outcomes of uncontrolled, nonrandomized trials, or from observational studies. Grade D recommendations were used only in cases where some guidance was needed but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. Grade D recommendations were made by Panel Consensus and were based on clinical experience or knowledge that does not meet the above-listed criteria.6

Smoking cessation recommendations were not graded.

- In patients who smoke, smoking cessation is very important. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- First-line pharmacotherapies for tobacco dependence—varenicline, bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch—are effective and at least one of these medications should be prescribed in the absence of contraindications.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
The FDA updated their recent safety alert concerning the use of varenicline and major adverse cardiovascular events (MACE). In June 2011, the FDA cautioned the public about the possibility of a connection between MACE and varenicline use; the evidence for the caution was based on a single study. Because of this, the FDA asked the manufacturer of varenicline to conduct a meta-analysis to determine any extent of MACE with varenicline use. This current safety alert from December 2012 reports the results of the meta-analysis which included 15 trial and 7,002 subjects. The meta-analysis found there was an overall low incidence of MACE during treatment or within 30 days post treatment (0.31% varenicline subjects vs. 0.21% placebo subjects) and the difference between treatment groups was not statistically significant (hazard ratio 1.95; 95% CI 0.79 to 4.82). Therefore, the FDA advises health care professionals to weigh the risks of varenicline against the benefits of its use; be aware that smoking is a major risk factor for cardiovascular disease; and that varenicline is effective at helping patients quit smoking and remain abstinent for as long as one year.7

New Trials (Appendix 1):
A total of 213 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Cinciripini et al conducted a twelve week randomized control trial comparing the efficacy of varenicline, bupropion sustained release (SR) and placebo on smoking abstinence. Patients (n=294) were randomized to one of the three treatment cohorts; all patients also received intensive counseling on smoking cessation over 10 sessions for a total of 240 minutes of counseling over the duration of the clinical trial. The study’s primary outcome was long-term abstinence.
from smoking measured at three and six months post quit date. Abstinence rates were significantly higher for bupropion SR versus placebo patients at the end of treatment (OR 2.77; 95% CI 1.48 to 5.20) and at three months (OR 2.90; 95% CI 1.52 to 5.54), but not at six months (OR 1.77; 95% CI 0.86 to 3.62). Patients on varenicline were significantly more likely to remain tobacco abstinent than those on placebo at the end of treatment (OR 3.92; 95% CI 2.06 to 7.47), at three months (OR 3.69; 95% CI 1.90 to 7.16), and at six months (OR 2.35; 95% CI 1.1 to 4.83). There was no significant difference between rates of tobacco abstinence between varenicline and bupropion SR patients at the end of treatment (OR 1.41; 95% CI 0.79 to 2.42), three months (OR 1.27; 95% CI 0.71 to 2.28), or six months (OR 1.33; 95% CI 0.68 to 2.58). Overall rates of adverse events were similar between treatment groups: varenicline 86.1%, bupropion 80.4%, and placebo 79.0%. No significant group differences were reported for any of the psychiatric or neurological adverse events, including anxiety, irritability, depression, emotional lability, and disturbances in attention. Cardiovascular adverse events were highest in the placebo group. This was a high quality study.8

Ferkitech et al conducted a twelve week trial comparing tobacco abstinence rates for varenicline versus combination patch and gum nicotine replacement therapy (NRT). Patients with HIV and a tobacco habit were directed to treatment with varenicline (n=118) or NRT (n=110) dependent on patient preference or psychiatric history; patients with comorbid psychiatric illness were given NRT. All patients received 12 weeks of telephone smoking cessation counseling. The primary endpoint was tobacco abstinence at three months after the end of the trial. Abstinence was counted by measuring salivary cotinine and expired air carbon monoxide. Patients on varenicline were significantly more likely to remain tobacco abstinent at the end of three months than the NRT patients (OR 2.72; 95% CI 1.50 to 4.94). Adverse events were higher in the varenicline cohort than the NRT group. Discontinuations due to adverse events were much higher for varenicline versus NRT patients (14.4% vs 1.8%). This was a low quality trial with many opportunities for bias to compromise the results. No randomization, blinding or allocation concealment was conducted. Trial conductors had a more favorable view of varenicline efficacy over NRT which was made evident by their encouraging patients to use varenicline over NRT.9
References:


## Smoking Cessation

### Goal(s):

- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products

### Requires PA:
- Non-preferred products
  - NRT beyond 6 month in the absence of behavioral counseling
  - Varenicline beyond 12 weeks

### Length of Authorization: 3-6 months

<table>
<thead>
<tr>
<th>Approval Criteria: Nicotine Replacement Therapy (NRT)</th>
<th>Record ICD-9 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the diagnosis?</td>
<td></td>
</tr>
<tr>
<td>2. Is the diagnosis for tobacco dependence? (ICD-9 305.1)?</td>
<td>Yes: Go to #3</td>
</tr>
<tr>
<td></td>
<td>No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
<tr>
<td>3. Is the request for a preferred NRT?</td>
<td>Yes: Go to #6</td>
</tr>
<tr>
<td></td>
<td>No: Go to #4</td>
</tr>
<tr>
<td>4. Is the request for varenicline?</td>
<td>Yes: Go to #5.</td>
</tr>
<tr>
<td></td>
<td>No: Go to #7</td>
</tr>
<tr>
<td>5. Has patient quit?</td>
<td>Yes: Approve varenicline x 12 additional weeks.</td>
</tr>
<tr>
<td></td>
<td>No: Go to #6</td>
</tr>
<tr>
<td>6. Is the patient enrolled in a smoking cessation behavioral counseling program (e.g. Quit Line at: 800 – xxx-xxxx).</td>
<td>Yes: Approve NRT x 6 additional months or Approve varenicline x 12 additional weeks.</td>
</tr>
<tr>
<td></td>
<td>No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
<tr>
<td></td>
<td>No: Go back to #6</td>
</tr>
</tbody>
</table>

### Message:

- Preferred products do not require a PA for initial treatment.
- Preferred products are evidence based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. Reports are available at: [http://pharmacy.oregonstate.edu/drug_policy/reviews](http://pharmacy.oregonstate.edu/drug_policy/reviews)
Appendix 2: Abstracts of Randomized Control Trials


**Importance:** Given the actions of varenicline tartrate and bupropion hydrochloride sustained-release (SR) on neurobiological targets related to affect and reward, it is thought that the modulation of nicotine withdrawal symptoms may contribute to their effectiveness.

**Objective:** To assess the relative efficacy of varenicline and bupropion SR plus intensive counseling on smoking cessation and emotional functioning.

**Design and Setting:** Placebo-controlled randomized clinical trial at a university medical center.

**Participants:** In total, 294 community volunteers who wanted to quit smoking.

**Interventions:** Twelve weeks of varenicline, bupropion SR, or placebo plus intensive smoking cessation counseling (10 sessions, for a total of approximately 240 minutes of counseling).

**Main Outcome Measures:** Prolonged abstinence from smoking and weekly measures of depression, negative affect, and other symptoms of nicotine withdrawal.

**Results:** Significant differences were found in abstinence at the end of treatment and through the 3-month post quit follow-up visit, favoring both active medications compared with placebo. At the 6-month post quit follow-up visit, only the varenicline vs placebo comparison remained significant. Varenicline use was also associated with a generalized suppression of depression and reduced smoking reward compared with the other treatments, while both active medications improved concentration, reduced craving, and decreased negative affect and sadness compared with placebo, while having little effect (increase or decrease) on anxiety and anger. No differences were noted in self-reported rates of neuropsychiatric adverse events.

**Conclusions and Relevance:** In a community sample, varenicline exerts a robust and favorable effect on smoking cessation relative to placebo and may have a favorable (suppressive) effect on symptoms of depression and other affective measures, with no clear unfavorable effect on neuropsychiatric adverse events.


**Introduction:** The prevalence of smoking is high among the human immunodeficiency virus (HIV)-infected population, yet there are few studies of tobacco dependence treatment in this population. This paper reports the safety of varenicline versus nicotine replacement therapy (NRT) and describes preliminary results about the effectiveness of varenicline versus NRT in HIV-infected smokers.

**Methods:** Participants completed 12 weeks of telephone counseling and either varenicline or NRT. Varenicline was encouraged as the preferred intervention; NRT was used for those unable/unwilling to take varenicline. Adverse events (AEs), related to pharmacotherapy, were monitored. Biochemically confirmed abstinence at 3 months was examined. Inverse probability of treatment weighted logistic regression models was fit to compare participants on varenicline to those on NRT.

**Results:** Among participants on varenicline (n = 118), the most common AEs were nausea, sleep problems, and mood disturbances. One person reported suicidal ideation; there were no cardiovascular complications. There were no differences in the varenicline AE profile between participants on combination antiretroviral therapy (ART) and those not on ART. The percentages of confirmed abstainers were 11.8% in the NRT group and 25.6% in the varenicline group. The odds of being abstinent were 2.54 times as great in the varenicline group compared with the NRT group in the propensity weighted model (95% CI 1.43–4.49).

**Conclusions:** In this preliminary study, the safety profile of varenicline among HIV-infected smokers resembles findings among smokers without HIV. In addition, varenicline may be more effective at promoting abstinence in this population. Future randomized clinical trials are warranted.
Month/Year of Review: March 2014  
Date of Last Review: 2009  
PDL Classes: Pulmonary- Asthma Rescue  
Source Document: Health Resources Commission

Current Status of PDL Class:
- Preferred Agents: ALBUTEROL SULFATE SOLUTION/VIAL-NEB, PIRBUTEROL ACETATE, ALBUTEROL HFA (PROAIR HFA®)
- Non-preferred Agents: LEVALBUTEROL MDI/NEBULIZER

Previous Conclusions Recommendations:
- In adults and children with asthma and adults with COPD there is insufficient evidence to determine relative differences in efficacy or effectiveness between albuterol and levalbuterol.
- There is insufficient evidence to determine a relative difference in safety or adverse events with these medications.
- There is insufficient evidence to determine comparative differences in efficacy or effectiveness in subgroups of patients’ base on demographics, other medications, comorbidities, or pregnancy.
- There is insufficient evidence to determine comparative differences in heart rate or tremor for predominantly older male patients for albuterol vs. levalbuterol.

Research Questions:
- Is there any new comparative evidence of different short acting beta2- agonists?
- Is there any new comparative safety data of short acting beta2- agonists?
- Are there subpopulations of patients for which one medication or formulation is more effective or associated with fewer adverse effects?

Methods:
The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.¹

Conclusions and Recommendations:
- No further review or research needed at this time; update PA criteria.
- Evaluate comparative costs in executive session.

References:
Drug Class Review
on
Quick-relief Medications for Asthma

Preliminary Scan Report #3

November 2013

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the
comparative effectiveness and safety profiles of different drugs within
pharmaceutical classes. Reports are not usage guidelines, nor should they
be read as an endorsement of, or recommendation for, any particular drug,
use or approach. Oregon Health & Science University does not recommend
or endorse any guideline or recommendation developed by users of these
reports.

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

Scan prepared by Shelley S. Selph, MD

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Portland, Oregon 97239. All rights reserved.
OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations’ consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA since the last report. Other important studies could exist.

Date of Last Update Report:

Update #1 was completed in October 2008, with searches through May 2008.

Date of Previous Scans:

Scan #1: October 2009
Scan #2: September 2010

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
2. What is the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
3. Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm, differ in efficacy, effectiveness, or frequency and severity of adverse events?
Inclusion criteria

Populations

1. Adults or children with asthma including those with exercise-induced bronchospasm

Excluded populations:

1. COPD
2. Acute bronchitis
3. Bronchiectasis
4. Children < 2 years with recurrent or persistent wheezing
5. Cystic fibrosis
6. High-altitude pulmonary edema

Interventions

1. Inhaled short-acting beta$_2$-agonists (SABA)
   a. Albuterol (salbutamol in Canada) MDI and nebulizer solution
   b. Levalbuterol (R-albuterol) MDI and nebulizer solution (levalbuterol is not available in Canada)
   c. Pirbuterol (not available in Canada)
   d. Terbutaline: available only in Canada
   e. Fenoterol: available only in Canada
2. Short-acting anticholinergics
   a. Ipratropium bromide MDI and nebulizer solution
3. Combination products
   a. Ipratropium bromide with albuterol MDI or ipratropium bromide with albuterol nebulizer solution

Excluded interventions

1. Systemic corticosteroids
   a. Prednisone
   b. Methylprednisolone
   c. Prednisolone
2. Inhaled Corticosteroids
3. Inhaled Cromolyn
4. Salmeterol
5. Long-acting anticholinergics: tiotropium
6. Studies where bronchospasm was induced by methacholine, histamine, cold
7. Combination products which include a quick-relief agent and another agent not included in this review
8. Formoterol

Comparators

1. Head-to-head studies examining the above bronchodilators
Excluded comparators
   1. Comparisons to other drugs or to placebo (to achieve indirect comparisons)

**Effectiveness Outcomes**

   1. Symptoms: e.g., cough, wheezing, shortness of breath
   2. Change in treatment regimen for the exacerbation
   3. Healthcare utilization: length of stay in the ER or other clinical facility, need for re-treatment within 24 hours, hospital admissions, length of hospital stay
   4. For exercise induced bronchospasm: exercise tolerance, symptoms
   5. Mortality

**Harms Outcomes**

   1. Overall adverse events reported
   2. Withdrawals due to adverse events
   3. Serious adverse events

**Setting**

   1. Outpatient settings including urgent care facilities and the emergency room

**Study Designs**

   1. For effectiveness: Head-to-head RCTs or controlled clinical trials with total sample size ≥ 20. No minimum duration of follow-up.
   2. For adverse events: Head-to-head RCTs, controlled clinical trials, or observational studies with sample size ≥ 10. No minimum duration of follow-up.

**METHODS**

**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2010 through October Week 3 2013, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) web site for identification of new drugs, indications, and safety alerts and Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/index.php/en/home) and Agency for Healthcare Research and Quality (http://www.ahrq.gov/clinic/epcindex.htm#lung) for Comparative Effectiveness Reviews.

**Study Selection**

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.
RESULTS

New Drugs/Indications

No new drugs or indications were identified.

New Boxed Warnings

No new boxed warnings were identified.

Comparative Effectiveness Reviews

No new comparative effectiveness reviews were identified.

Randomized Controlled Trials

Searches resulted in 128 potentially relevant citations. Of those, 8 new trials meeting inclusion criteria were identified. (See Table 1) One new head-to-head trial compared racemic albuterol nebulizer treatment with levalbuterol nebulizer treatment. Five head-to-head studies compared different delivery methods of the same drug (e.g., with or without a spacer, nebs vs MDI, delivery by mask vs by hood). One relevant placebo-controlled and one active-controlled trial were also identified. (See Appendix A for abstracts of included studies)

Table 1. Potentially relevant trials of drugs for quick relief of asthma symptoms

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Comparison</th>
<th>N</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-to-head drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrews 2009</td>
<td>Levalbuterol nebs</td>
<td>81</td>
<td>Children aged 6-18</td>
</tr>
<tr>
<td></td>
<td>Racemic albuterol nebs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punj 2009</td>
<td>Levosalbutamol</td>
<td>60</td>
<td>Children aged 5-18</td>
</tr>
<tr>
<td></td>
<td>Racemic Salbutamol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilkinson 2011</td>
<td>Racemic albuterol nebs</td>
<td>99</td>
<td>Children aged 6-17</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol nebs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head-to-head delivery method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar-Yishay 2011</td>
<td>Salbutamol 0.30 mg/kg by mask</td>
<td>26</td>
<td>Wheezy infants</td>
</tr>
<tr>
<td></td>
<td>Salbutamol 0.30 mg/kg by hood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direkwatanachai 2011</td>
<td>Salbutamol pMDI 6 puffs with Volumatic spacer</td>
<td>216</td>
<td>Children aged 5-18 in Thailand</td>
</tr>
<tr>
<td>Study Year</td>
<td>Comparison</td>
<td>N</td>
<td>Focus</td>
</tr>
<tr>
<td>------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Dhuper 2011</td>
<td>Salbutamol 6 puffs with Easyhaler (DPI)</td>
<td>60</td>
<td>Inner city adults; crossover study</td>
</tr>
<tr>
<td>Rotta 2010</td>
<td>Salbutamol pMDI with spacer</td>
<td>46</td>
<td>Children aged 1-5</td>
</tr>
<tr>
<td>Sabato 2011</td>
<td>1 hour of continuous nebulized albuterol</td>
<td>149</td>
<td>Children aged 0-18</td>
</tr>
<tr>
<td></td>
<td>1-time albuterol treatment with AeroEclipse breath-actuated nebulizer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler 2011</td>
<td>Albuterol inhaler</td>
<td>46</td>
<td>Crossover study</td>
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<tr>
<td></td>
<td>Placebo inhaler</td>
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<td></td>
</tr>
<tr>
<td>Active-controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mangunnegoro 2011</td>
<td>Salbutamol nebs (1 ampule)</td>
<td>140</td>
<td>Indonesians with moderate acute asthma age 15-60</td>
</tr>
<tr>
<td></td>
<td>Procaterol nebs (1 ampule)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous scans identified two head-to-head trials comparing levalbuterol with albuterol in a pediatric population, for a total of 10 new studies published since the last update. Of these, three studies compared one included drug with another included drug; all three compared racemic albuterol with levalbuterol in children (combined N=240).
APPENDIX A. Abstracts of potentially relevant new trials for quick relief of asthma symptoms (N=8)

Head-to-head trials (drug vs drug, N=3)


OBJECTIVE: To assess the use of high-dose continuous levalbuterol (LEV), the single active (R)-enantiomer of racemic albuterol (RAC), in the treatment of status asthmaticus. STUDY DESIGN: Children age 6 to 18 years with severe asthma exacerbation were enrolled in this randomized, double-blind trial if they failed initial emergency department (ED) therapy with RAC and systemic steroids. Subjects received equipotent doses of RAC (20 mg/hour) or LEV (10 mg/hour) within a standardized inpatient protocol. Blood samples for measurements of albuterol enantiomer, potassium, and glucose levels were obtained from the first 40 subjects. The median time until discontinuation of continuous therapy was compared using the rank-sum test, and other outcomes were compared using general linear mixed models. RESULTS: A total of 81 subjects (40 in the RAC group and 41 in the LEV group) were enrolled; the 2 groups were similar at baseline. Both groups tolerated continuous therapy with similar changes in heart rate and serum potassium and glucose levels but higher serum (S)-albuterol concentrations in the subjects treated with RAC. The median time for continuous therapy was similar in the RAC and LEV groups (18.3 hours vs 16.0 hours), as were the other clinical measures. CONCLUSIONS: Substituting high-dose continuous LEV for RAC did not reduce the time on continuous therapy and had similar adverse effects in children who had failed initial treatment with RAC.


OBJECTIVE: To compare efficacy and tolerability of levosalbutamol (Group 1) and racemic salbutamol (Group 2) for the treatment of acute exacerbation of asthma in children age 5 to 18 yr. METHODS: A randomized double blind clinical study involving 60 children was undertaken between October' 06 to December' 07. RESULTS: The following baseline clinical characteristic were recorded initially and after giving 3 nebulizations at 20 min intervals in the 1st hour of presentation viz respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO2, PEFR (peak expiratory flow rate), serum K+ level and asthma score. In Group 1 patients (levosalbutamol), there was significant increment in SPO2 and PEFR (P CONCLUSION: Levosalbutamol appears to be more efficacious than racemic salbutamol in terms of improvement in PEFR, SPO2 and asthma score while deleterious effects of tachycardia and fall in serum K+ were seen with racemic salbutamol.

OBJECTIVE: To compare racemic albuterol (RAC) with levalbuterol (LEV) in continuous form for the treatment of acute pediatric asthma exacerbations in the emergency department.

STUDY DESIGN: Children between the ages of 6 and 17 inclusive were enrolled if they had a history of asthma, presented to the emergency department with an acute asthma exacerbation, and had an initial forced expiratory volume in 1 second (FEV1) <70% predicted. Patients were then randomized to receive either 7.5 mg of RAC or 3.75 mg of LEV over 1 hour, in addition to standard asthma therapies. Spirometry and asthma scoring were performed at the end of the first hour, and a second hour-long nebulization with the same drug was administered if deemed necessary. Spirometry and asthma scoring were again performed and the final disposition was recorded. As a second, optional part of the study, baseline serum albuterol levels were collected on some patients before treatment.

RESULTS: A total of 99 patients completed the study (44 RAC and 55 LEV). Baseline characteristics were similar except that the RAC group had a higher baseline asthma score. Children in the RAC group had a greater improvement in their FEV1 (p = .043) as well as in their asthma scores (p = .01) after 1 hour of continuous treatment compared to the LEV group. The greater improvement in asthma scores was maintained after the second hour of continuous therapy in the RAC group (p = .008) but not for FEV1 measurements (p = .57). There were no differences between groups for changes in heart rate, respiratory rate, oxygen saturation, or rates of admission.

CONCLUSIONS: At the doses used, RAC appears to be superior to LEV with respect to changes in FEV1 and asthma score. There was no significant difference between the drugs with respect to admission rates or side-effect profile.

Head-to-head trials (delivery method vs delivery method, N=5)


BACKGROUND: In infants, small volume nebulizers with a face mask are commonly used to facilitate aerosol therapy. However, infants may be disturbed by mask application, causing poor mask-to-face seal and thus reducing the dose delivered.

OBJECTIVES: To compare lung function response to bronchodilator nebulization via two delivery devices: hood versus mask.

METHODS: We studied 26 recurrently wheezy infants aged 45.8 weeks (95% confidence interval 39.6-52.0). Inhalations of 0.30 mg/kg salbutamol were administered in two alliqots 30 minutes apart using mask and hood in alternating order (M+H or H+M). Response to inhalations was measured by maximal
expiratory flows at functional residual capacity (V’maxFRC) at 5 minute intervals after each dose, and area under the V’maxFRC curve (AUC) was documented.

RESULTS: A small but significant response to salbutamol was observed following the second inhalation with V’maxFRC, improving by 31.7% (7.2-56.2, P (0.02) and AUC by 425% x min (-154, 1004; P < 0.02). The improvement following salbutamol was similar by both delivery modalities but with a small but significantly better response when H was used after M (P < 0.01).

CONCLUSIONS: Nebulized salbutamol induced a variable but positive response in wheezy infants. Salbutamol via hood was as effective as conventional face mask delivery. Since it is simple and patient-friendly, it could replace the face mask method particularly with uncooperative infants.


BACKGROUND: Beta(2) agonist administered via a nebulizer is the standard treatment for acute asthma exacerbation. There are some limitations for the use of nebulization. We conducted a study to determine the efficacy of salbutamol administered via the pMDI with Volumatic spacer and the Easyhaler (DPI) compared to nebulization in mild to moderate asthma exacerbations in children.

METHODS: A multicenter, randomized, controlled study was conducted in children between 5 and 18 years of age who presented at an emergency or outpatient department. They were randomized to receive either 6 puffs of salbutamol via the pMDI with Volumatic spacer, or via the Easyhaler, or 0.15 mg/kg of salbutamol nebulized via oxygen (or compressed air). The primary outcome was the clinical response which was assessed using the modified Wood's asthma score. The secondary outcomes were: hospitalization, asthma revisit within 3 days, systemic corticosteroid use and adverse events. The clinical score, oxygen saturation, PR, RR, BP and adverse events were recorded at time 0 (before treatment) and 20, 40 and 60 minutes after drug administration.

RESULTS: There were no statistically significant differences in the clinical response between the three groups at the 1st, 2nd or 3rd dose or for the SpO(2) or the respiratory rate while the children in the Easyhaler group had significantly less tachycardia after the 2nd dose. No significant adverse events were noted among the three groups.

CONCLUSIONS: Salbutamol administered via pMDI with Volumatic spacer or DPI (Easyhaler) are as effective as salbutamol given via a nebulizer in providing effective relief of mild to moderate severity acute asthma exacerbation in children between 5 and 18 years of age.

Dhuper S. Chandra A. Ahmed A. Bista S. Moghekar A. Verma R. Chong C. Shim C. Cohen H. Choksi S. Efficacy and cost comparisons of bronchodilatator administration

BACKGROUND: Despite demonstration of equivalent efficacy of beta agonist delivery using a metered dose inhaler (MDI) with spacer vs. nebulizer in asthma patients, use of a nebulizer remains standard practice.

OBJECTIVES: We hypothesize that beta agonist delivery with a MDI/disposable spacer combination is an effective and low-cost alternative to nebulizer delivery for acute asthma in an inner-city population.

METHODS: This study was a prospective, randomized, double-blinded, placebo-controlled trial with 60 acute asthma adult patients in two inner-city emergency departments. Subjects (n = 60) received albuterol with either a MDI/spacer combination or nebulizer. The spacer group (n = 29) received albuterol by MDI/spacer followed by placebo nebulization. The nebulizer group (n = 29) received placebo by MDI/spacer followed by albuterol nebulization. Peak flows, symptom scores, and need for rescue bronchodilator were monitored. Median values were compared with the Kolmogorov-Smirnov test.

RESULTS: Patients in the two randomized groups had similar baseline characteristics. The severity of asthma exacerbation, median peak flows, and symptom scores were not significantly different between the two groups. The median (interquartile range) improvement in peak flow was 120 (75-180) L/min vs. 120 (80-155) L/min in the spacer and nebulizer groups, respectively (p = 0.56). The median improvement in the symptom score was 7 (5-9) vs. 7 (4-9) in the spacer and nebulizer groups, respectively (p = 0.78). The median cost of treatment per patient was $10.11 ($10.03-$10.28) vs. $18.26 ($9.88-$22.45) in the spacer and nebulizer groups, respectively (p < 0.001).

CONCLUSION: There is no evidence of superiority of nebulizer to MDI/spacer beta agonist delivery for emergency management of acute asthma in the inner-city adult population. MDI/spacer may be a more economical alternative to nebulizer delivery.


OBJECTIVE: The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used.

METHOD: A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21 children received salbutamol by nebulization (150 microg/kg), three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or
nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% (P < 0.05).

RESULTS: No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in patients >2 years vs patients < or =2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference (P = 0.05).

CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the bioavailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.


BACKGROUND: Bronchodilator treatment for asthma can be provided with various aerosol-generating devices and methods. There have been no randomized trials of a breath-actuated nebulizer versus continuous 1-hour nebulization and/or small-volume constant-output nebulizer in pediatric asthma patients.

METHODS: We conducted a randomized study of one-time albuterol treatment with the AeroEclipse breath-actuated nebulizer versus standard therapy (single treatment via small-volume nebulizer or 1-hour of continuous nebulized albuterol) in pediatric asthma patients in the emergency department. Eligible patients were those admitted to the emergency department, 0 months to 18 years of age, who presented with asthma or wheezing. We assessed all the patients with our clinical asthma scoring system and peak-flow measurement if possible. We stratified the patients by clinical asthma score and weight, and then randomized them to receive their initial albuterol treatment in the emergency department via either AeroEclipse or standard therapy. We recorded time in the emergency department, change in clinical asthma score, need for additional bronchodilator treatments, need for admission, patient response, ability to actuate the AeroEclipse, and adverse effects.

RESULTS: We enrolled 149 patients between October 14, 2004 and November 11, 2005, and we randomized 84 patients to AeroEclipse and 65 to standard therapy. The cohort's average age was 5.5 years. There were no significant differences in demographics. The initial mean clinical asthma scores were 5.1 +/- 2.4 in the AeroEclipse group, and 5.1 +/- 2.1 in the standard-therapy group. Time in the emergency department was not different (AeroEclipse 102 min, standard therapy 125 min, P = .10), but the AeroEclipse group had a significantly greater improvement in clinical asthma score (1.9 +/- 1.2 vs 1.2 +/- 1.4, P = .001) and respiratory rate (P = .002), and significantly lower admission rate (38% vs 57%, P = .03). There was no difference in adverse effects.

CONCLUSIONS: Although AeroEclipse did not reduce the time in the ED, it significantly improved clinical asthma score, decreased admissions, and decreased respiratory rate.
Placebo-controlled trial (N=1)


BACKGROUND: In prospective experimental studies in patients with asthma, it is difficult to determine whether responses to placebo differ from the natural course of physiological changes that occur without any intervention. We compared the effects of a bronchodilator, two placebo interventions, and no intervention on outcomes in patients with asthma.

METHODS: In a double-blind, crossover pilot study, we randomly assigned 46 patients with asthma to active treatment with an albuterol inhaler, a placebo inhaler, sham acupuncture, or no intervention. Using a block design, we administered one each of these four interventions in random order during four sequential visits (3 to 7 days apart); this procedure was repeated in two more blocks of visits (for a total of 12 visits by each patient). At each visit, spirometry was performed repeatedly over a period of 2 hours. Maximum forced expiratory volume in 1 second (FEV(1)) was measured, and patients' self-reported improvement ratings were recorded.

RESULTS: Among the 39 patients who completed the study, albuterol resulted in a 20% increase in FEV(1), as compared with approximately 7% with each of the other three interventions (P<0.001). However, patients' reports of improvement after the intervention did not differ significantly for the albuterol inhaler (50% improvement), placebo inhaler (45%), or sham acupuncture (46%), but the subjective improvement with all three of these interventions was significantly greater than that with the no-intervention control (21%) (P<0.001).

CONCLUSIONS: Although albuterol, but not the two placebo interventions, improved FEV(1) in these patients with asthma, albuterol provided no incremental benefit with respect to the self-reported outcomes. Placebo effects can be clinically meaningful and can rival the effects of active medication in patients with asthma. However, from a clinical-management and research-design perspective, patient self-reports can be unreliable. An assessment of untreated responses in asthma may be essential in evaluating patient-reported outcomes.

Active-controlled trial (N=1)


OBJECTIVE: 2 agonists have been used widely as relievers in asthma management. Procaterol is a selective 2 agonist, claimed to be more selective than salbutamol. The present study aimed to compare the efficacy of nebulized procaterol with nebulized salbutamol in the treatment of moderate acute asthma.

METHODS: This was a randomized, double-blind, parallel group study in 140 patients with moderate acute asthma according to modified GINA 1998 who visited emergency department of Persahabatan Hospital, Jakarta. Patients were randomly
assigned to receive three doses of either nebulized procaterol or salbutamol. The primary efficacy variable was the improvement in predicted peak expiratory flow rate (PEFR), while the secondary efficacy variable was the improvement in asthma score and the incidence and severity of adverse events. This study is registered at Current Controlled Trials, number ISCTRIN25669625.

RESULTS: Baseline characteristics were similar in both groups. After treatment, there were significant improvement of % PEFR (p < 0.001) and asthma score (p < 0.001) in procaterol (n = 68) and salbutamol (n = 69) groups. It was shown that procaterol and salbutamol produced similar efficacy in improving % predicted PEFR and decreasing asthma score. Both treatments were well tolerated. Palpitation and sinus tachycardia were found as adverse events with low incidence.

CONCLUSION: In moderate acute asthma, nebulized procaterol and nebulized salbutamol were both effective in improving PEFR and decreasing asthma score. Both treatments were well tolerated, adverse reactions were rare.
Month/Year of Review: March 2014

Date of Last Review: September 2013

PDL Classes: Long-Acting Opioid Analgesics

Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- **Preferred Agents:** FENTANYL ER TRANSDERMAL FILM (DURAGESIC®), MORPHINE SULFATE ER (MS CONTIN®)
- **Non-preferred Agents:** BUPRENORPHINE ER TRANSDERMAL FILM (BUTRANS®), HYDROMORPHONE ER (EXALGO®), LEVORPHANOL, METHADONE, MORPHINE SULFATE ER (AVINZA®, KADIAN®), MORPHINE SULFATE/NALTRESONE ER (EMBEDA®), OXYCODONE ER (OXYCONTIN®), OXYMORPHINE ER (OPANA ER®), TRAMADOL ER (NUCYNTA®), TRAMADOL ER (ULTRAM ER®, CONZIP®)

Previous Conclusions Recommendations:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.
- Remove methadone from preferred status due to safety concerns.
- A form of morphine ER should remain a preferred option.
- There is insufficient evidence to establish difference in effectiveness or safety of tramadol ER versus the other LAOs.

PA Criteria: There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20 mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims (Appendix 1).

Research Questions:

- Is there any new comparative evidence on LOA’s
- Is there any new comparative safety data of LOA’s
- Are there subpopulations of patients for which one medication or formulation is more effective or associated with fewer adverse effects?

Methods:
The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.¹

Conclusions and Recommendations:

- There is insufficient comparative evidence to establish differences in effectiveness of hydrocodone ER (Zohydro® ER) versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of hydrocodone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER from the other LAOs.
- Maintain hydrocodone ER as non-preferred and evaluate comparative costs in executive session.
New Formulations:
Hydrocodone bitartrate ER oral capsule (Zohydro® ER) was FDA approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in October 2013. Because of the risks of addiction, abuse, and misuse, and the extended-release formulation, it should be reserved for use in patients for whom alternative treatment options (non-opioids or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate. Hydrocodone ER is a Schedule II controlled substance and the first FDA-approved single-entity (not combined with an analgesic such as acetaminophen) and extended-release hydrocodone product. It will be part of the ER/LA Opioid analgesics Risk Evaluation and Mitigation Strategy (REMS).

The efficacy of hydrocodone ER is based on one randomized, double-blind, placebo-controlled unpublished study of patients with chronic low back pain (n=302). Subjects were eligible if they had moderate to severe chronic low back pain present for at least several hours a day for a minimum of 3 months, required around-the-clock opioid therapy, were taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day, and had an average clinic pain score of 4 or greater on the numerical rating scale. Subjects with a history of illicit substance or alcohol abuse in the past 5 years or history of opioid abuse were excluded. The primary efficacy endpoint was change from baseline in average pain intensity on the 11-point scale as recorded in an electronic diary compared to placebo. There was high attrition through the study; although the primary efficacy analysis was done in the intention to treat population. The change from baseline in average daily pain score was 0.48 in the hydrocodone group and 0.96 in the placebo group (p=0.008). The specific results for the secondary endpoints were not provided in the FDA review document. This study remains unpublished and cannot be adequately assessed for quality and risk of bias.

Discontinuations due to adverse events occurred in about 10% of patients in both groups in the titration phase, with the most common adverse events being nausea, somnolence, constipation, vomiting, and headache. They occurred in 6.4% of patients during the treatment phase and 10.6% in the placebo group. The most common adverse events were consistent with the opioid class of drugs and include constipation, nausea, somnolence, fatigue, headache, and dizziness.

References:
3. Food and Drug Administration. Center for Drug Evaluation and Research. Summary Review: Application Number: 202880Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf
Appendix 1: Prior Authorization Criteria

**Opioid Analgesics – High Dose**

**Goal(s):**
- Limit the use of high dose opioid therapy to above-the-line diagnoses that are supported by the medical literature
- Limit the use of non-preferred products
- Promote the safe use of opioids.
  - Opioids have been associated with an increasing proportion of deaths in Oregon and the US.
  - Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)
  - Opioid deaths in Oregon are often associated with patients with a history of drug abuse.
  - Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventilation.
    - This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metabolism of methadone or fentanyl.
  - See Oregon DUR Board newsletter at:

**Initiative:**
Long and Short Acting Opioid quantity and dose limits: preferred agents, approved indications, and dose limits.

**Length of Authorization:**
Up to 6 months

**Covered Alternatives:**
A list of preferred opioids is available at [www.orpdl.org](http://www.orpdl.org)

**Requires a PA:**
- All non-preferred opioids and preferred opioids exceeding the dose threshold in the table below, not to exceed a Morphine Equivalent Dose (MED) of 120mg per day.
- Patient with terminal diagnosis, hospice, and metastatic neoplasm (ICD9 = 190xx – 199xx) are exempt from the PA requirements.

-Approved Prior Authorizations may be subject to quantity limits

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose threshold</th>
<th>Recommended starting dose for opioid-naive patients</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>20mcg/hour</td>
<td>5mcg/hr patch q 7 days</td>
<td>May increase dose q72 hours patients up to a max of 20mcg/hr q 7 days. Doses &gt;20mcg/hr q7 days increase risk of QTc prolongation.</td>
</tr>
<tr>
<td>Transdermal</td>
<td>(q 7 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50mcg/hour</td>
<td>Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>(q 72 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>30mg per 24 hours</td>
<td>2mg q 4–6 hours</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>40mg per 24 hours</td>
<td>2.5-5mg BID – TID</td>
<td>Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.</td>
</tr>
</tbody>
</table>

Dosing Threshold adapted from Washington State Agency Medical Directors Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain 2010 ([www.agencymeddirectors.wa.gov](http://www.agencymeddirectors.wa.gov))

Date: March 2014
**Morphine**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Immediate-release:</th>
<th>Adjust dose for renal impairment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>120mg per 24 hours</td>
<td>10mg q 4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15mg q 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Oxycodone**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Immediate-release:</th>
<th>Sustained-release:</th>
</tr>
</thead>
<tbody>
<tr>
<td>80mg per 24 hours</td>
<td>5mg q 4–6 hours</td>
<td>10mg q 12 hours</td>
</tr>
</tbody>
</table>

*See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10day or 2500mg/day for 10 days or more)*

**Oxymorphone**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Immediate-release:</th>
<th>Sustained Release:</th>
</tr>
</thead>
<tbody>
<tr>
<td>40mg per 24 hours</td>
<td>5–10mg q 4–6 hours</td>
<td>10mg q 12 hours</td>
</tr>
</tbody>
</table>

*Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol.*

### Dosing Threshold for select short acting opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose threshold</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>800mg/day</td>
<td>Dosing limits based on combinations (e.g. acetaminophen, ibuprofen) may lower the maximum daily dose</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>120mg/day</td>
<td></td>
</tr>
</tbody>
</table>

### Common indications OHP does not cover:*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>ICD9 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of soft tissue (including Fibromyalgia)</td>
<td>729.0-729.2, 729.31-729.39, 729.4-729.9, V53.02</td>
</tr>
<tr>
<td>Acute and chronic disorders of spine without one of the following neurologic impairments:</td>
<td>721-724, except 723.3 739, 839.2, 847</td>
</tr>
<tr>
<td>a. Reflex loss</td>
<td></td>
</tr>
<tr>
<td>b. Dermatomal muscle weakness</td>
<td></td>
</tr>
<tr>
<td>c. Dermatomal sensory loss</td>
<td></td>
</tr>
<tr>
<td>d. EMG or NCV evidence of nerve root impingement</td>
<td></td>
</tr>
<tr>
<td>e. Cauda equina syndrome</td>
<td></td>
</tr>
<tr>
<td>f. Neurogenic bowel or bladder</td>
<td></td>
</tr>
<tr>
<td>See Prioritized List of Health Services Guideline Notes 37 and 41</td>
<td></td>
</tr>
</tbody>
</table>

*Covered diagnoses are dependent on funding levels. A list of currently funded diagnoses can be found at [http://www.oregon.gov/OHA/OHPR/HSC/current_prior.shtml](http://www.oregon.gov/OHA/OHPR/HSC/current_prior.shtml)*

### Approval Criteria

1. What is the patient’s diagnosis? Record ICD9
2. Is the request for methadone >100mg? Yes: Go to 3 No: Go to 5

Date: March 2014
3. Does the patient have any of the following QTc Risk Factors?
   - Family history of “long QTc syndrome”, syncope, sudden death
   - Potassium depletion primary or secondary to drug use (i.e. diuretics)
   - Concurrent use of C34 inhibitors or QTc prolonging drugs (see table below)
   - Structural heart disease, arrhythmias, syncope

   **Yes:** Go to 4
   **No:** Go to 5

4. Is this new therapy (i.e. no previous prescription for the same drug last month)?

   **Yes:** Pass to RPH; Deny, (Medical Appropriateness) Go over black box warning and offer alternatives (e.g. Fentanyl transdermal, morphine extended release).
   **No:** Pass to RPH, Approve for 30-60 days to allow time to taper or transition to alternative. Direct to DUR Newsletter for assistance. Refer to Rx “Lock-in” Program for evaluation and monitoring.

5. Is the patient being treated for any of the following:
   a. Oncology pain (ICD-9 338.3)
   b. Terminal diagnosis (<6 months)
   c. Hospice care

   **Yes:** Go to #6
   **No:** Go to #8

6. Is the requested medication a preferred agent?

   **Yes:** Approve for up to 6 months
   **No:** Go to #7

7. Will the prescriber consider a change to a preferred product?

   **Yes:** Inform provider of covered alternatives in class.
   **No:** Approve for up to 6 months

8. Will the prescriber consider a change to a preferred product not to exceed 120mg MED?

   **Yes:** Inform provider of covered alternatives in class.
   **No:** Go to #9

9. Is the diagnosis covered by the OHP?

   **Yes:** Go to #10
   **No:** Pass to RPh, Deny (Not Covered by the OHP) May approve for 30-60 days to allow for tapering

10. Is this new therapy (i.e. no previous prescription for the same drug, same dose last month)?

    **Yes:** Go to #11
    **No:** Go To #12

11. Does the total daily opioid dose exceed 120mg MED?

    **Yes:** Pass to RPh, Deny (Medical Appropriateness)

    In general, the total dose of opioid should not exceed 120mg MED Risks substantially increase at doses at or above 100mg MED.

    Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.

    **No:** Go to #12
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes:</th>
<th>No:</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Has the patient had a recent urinary drug screen (within the past 90 days)?</td>
<td>Go to #13</td>
<td>Pass to RPH: Deny (Medical Appropriateness) Recommend Urine Drug Screen</td>
</tr>
<tr>
<td>13. Is the patient seeing a single prescribing practice &amp; pharmacy for pain treatment (short and long acting opioids)?</td>
<td>Go To #14</td>
<td>Approve 30-90 days; Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.</td>
</tr>
<tr>
<td>14. Does the total daily opioid dose exceed 120mg MED?</td>
<td>Go to #15</td>
<td>Go to #16</td>
</tr>
<tr>
<td>15. Can the prescriber provide documentation of sustained improvement in both function and pain AND is prescriber is aware of additional risk factors (e.g. concurrent benzodiazepines, skeletal muscle relaxants, other LAO or history of drug abuse)?</td>
<td>Approve up to 6 months. Quantity Limits Apply, e.g.: Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day</td>
<td>Approve 30-90 days to allow for potential tapering of dose. Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.</td>
</tr>
<tr>
<td>16. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, and long-acting oxymorphone)?</td>
<td>Go to #17</td>
<td>Approve for up to 6 months</td>
</tr>
<tr>
<td>17. Is the duplication due to tapering or switching products?</td>
<td>Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.</td>
<td>Deny (Medical Appropriateness) May approve for taper only. Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.</td>
</tr>
</tbody>
</table>

_P&T or DUR Board Action:_ 2/23/12 (TDW), 11/17/11(KK); 12/3/09 (KS), 9/9/09(klk), 12/4/08klk, 3/19/09
_Revision(s):_ 6/21/12, 5/14/12; 1/1/12; 1/1/10
_Initiated:_ 7/1/09

**Date:** March 2014
Drug Class Review

Long-Acting Opioid Analgesics

Preliminary Scan Report 2

December 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Sujata Thakurta, MPA:HA
OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations rule in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies, including observational studies, could exist.

Date of Last Update Report

Update #6, July 2011 (searches through January 2011)

Date of Last Preliminary Update Scan Report

Scan 1, April 2013 (searches through April 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide the review:

1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic noncancer pain?

2. What is the comparative effectiveness of long-acting opioids compared with short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic noncancer pain?

3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic noncancer pain?

4. What are the comparative harms of long-acting opioids compared with short-acting opioids in adult patients being treated for chronic noncancer pain?
5. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status, type of pain, or comorbidities) with chronic noncancer pain for which one long-acting opioid is more effective or associated with fewer harms?

6. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status, type of pain, or comorbidities) with chronic noncancer pain for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?

**Inclusion Criteria**

**Populations**

The population included in the review was adult (18 years old or greater) patients with chronic noncancer pain. We defined chronic noncancer pain as continuous or recurring pain for at least 6 months. Cancer patients and patients with HIV were excluded from the review.

**Interventions**

**Table 1. Included drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Forms</th>
<th>Recommended usual dosing frequency (times per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Butrans™</td>
<td>ER transdermal film</td>
<td>Every 7 days</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic®</td>
<td>ER transdermal film</td>
<td>Every 72 hours</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Exalgo®</td>
<td>ER oral tablet</td>
<td>1</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Generic</td>
<td>Oral tablet</td>
<td>3-4</td>
</tr>
<tr>
<td>Methadone</td>
<td>Generic, Dolophine®</td>
<td>Oral tablet</td>
<td>2-3</td>
</tr>
<tr>
<td>Morphine</td>
<td>Generic</td>
<td>ER oral capsule</td>
<td>1</td>
</tr>
<tr>
<td>Avinza®</td>
<td>ER oral capsule</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kadian®</td>
<td>ER oral capsule</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MS Contin®</td>
<td>ER oral capsule</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Oramorph SR®</td>
<td>ER oral tablet</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate and naltrexone hydrochloride</td>
<td>Embeda™</td>
<td>ER oral capsule</td>
<td>1-2</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>OxyContin®</td>
<td>ER oral tablet</td>
<td>2</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Opana ER®</td>
<td>ER oral tablet</td>
<td>2</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Nucynta ER®</td>
<td>ER oral tablet</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocodone bitartrate</td>
<td>Zohydro™ER</td>
<td>ER oral capsule</td>
<td>2</td>
</tr>
</tbody>
</table>

| Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release. |
| Shading indicates drugs approved since the last update report. |
| *Discontinued |

**Study designs**

Effectiveness:
- Controlled clinical trials
• Good quality systematic reviews

Harms:
• Controlled clinical trials
• Good quality systematic reviews
• Comparative observational studies

Comparators
• Another long-acting opioid
• Another drug
• Placebo

Effectiveness outcomes
• Pain intensity
• Pain relief
• Function

Harms outcomes
• Overall withdrawals
• Withdrawals due to adverse events
• Risk of abuse and addiction, including death and hospitalization
• Specific adverse events (nausea, vomiting, constipation, dizziness, somnolence, confusion)

METHODS

Literature Search
To identify relevant citations, we searched Ovid MEDLINE from April 2013 to December 2013 using terms for included drugs. To identify trials of drugs not included in the last full report, we did not restrict the start date of the search. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.
Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

**Identified in this Preliminary Update Scan**
Hydrocodone bitartrate extended release oral capsule (Zohydro™ER): FDA approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (10/25/2013).

**Identified in previous Preliminary Update Scans**
Tapentadol extended release oral tablet (Nucynta ER®): FDA approved for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (8/25/2011).

New Indications

**Identified in this Preliminary Update Scan**
None.

**Identified in previous Preliminary Update Scans**
None

New Black Box Warnings

**Identified in this Preliminary Update Scan**
None

**Identified in previous Preliminary Update Scans**
None

Comparative Effectiveness Reviews

**Reviews identified in this Preliminary Update Scan**
There were several comparative effectiveness reviews (CERs) that were either published or were in progress (Table 1). Although it is not clear that these reviews evaluate long-acting drugs in the same way they are in the DERP report, details are included in Appendix A,

<table>
<thead>
<tr>
<th>Source</th>
<th>Author, year</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHRQ/EHCEPC report in progress</td>
<td>2013</td>
<td>Chronic Pain</td>
</tr>
<tr>
<td>AHRQ/EHC EPC report in</td>
<td>2013</td>
<td>Low Back Pain</td>
</tr>
</tbody>
</table>
progress

Preliminary Scan Report #2 | Drug Effectiveness Review Project
---|---

Long-acting opioids

**CADTH** | **6/2012** | Chronic Non-Cancer Pain
---|---|---

Rapid Response Report

**CADTH** | **10/2011** | Chronic Pain
---|---|---

Rapid Response Report

**CADTH** | **4/2012** | Drug Diversion and Misuse
---|---|---

Cochrane

**Chapparro, 2013** | **Chronic low-back pain**
---|---|---

Cochrane

**McNicoll, 2013** | **Neuropathic Pain**
---|---|---

Cochrane

**Haroutiunian, 2012** | **Chronic non-cancer pain in adults**
---|---|---

**Reviews identified in previous Preliminary Update Scans**

None.

**Controlled Clinical Trials**

**Trials identified since the most recent Full Report**

Cumulatively, we identified 5 head to head trials, 3 active-control trials and 7 placebo controlled trials that have been published since the last full update of this report. Medline searches for the most recent scan resulted in 243 citations. Of those, there were 5 potentially relevant new trials (see Table 2). Abstracts of these trials are attached in Appendix B. We identified 2 head-to-head trials on chronic noncancer pain and 3 placebo controlled trials in patients with low back pain or osteoarthritis. In the previous scan we identified 3 new head-to-head trials, all comparing tapentadol ER to oxycodone CR in patients with osteoarthritis or low back pain. Three trials compared a long-acting opioid to a short-acting opioid, and 4 trials compared an included drug to placebo.

**Table 2. New potentially relevant trials**

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Drug/Comparator</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head-to-Head Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afilalo 2010</td>
<td>Tapentadol ER vs oxycodone CR</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Buynak 2010</td>
<td>Tapentadol ER vs oxycodone CR</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Wild 2010</td>
<td>Tapentadol ER vs oxycodone CR</td>
<td>Osteoarthritis or low back pain</td>
</tr>
<tr>
<td>Mitra, 2013</td>
<td>Transdermal buprenorphine vs transdermal fentanyl</td>
<td>Persistent noncancer pain</td>
</tr>
<tr>
<td>Richarz, 2013</td>
<td>OROS Hydromorphone ER vs oxycodone CR</td>
<td>Chronic noncancer pain</td>
</tr>
<tr>
<td><strong>Active-control Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cruciani 2012</td>
<td>Hydromorphone ER vs hydromorphone IR</td>
<td>Not specified</td>
</tr>
<tr>
<td>Etropolski 2010</td>
<td>Tapentadol ER vs tapentadol IR</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Steiner 2011a</td>
<td>Buprenorphine transdermal system vs oxycodone IR</td>
<td>Low back pain</td>
</tr>
</tbody>
</table>
### Placebo Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Formulation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu, 2012</td>
<td>Morphine SR</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Rauck, 2013</td>
<td>OROS hydromorphone ER</td>
<td>Chronic osteoarthritis</td>
</tr>
<tr>
<td>Jamison, 2013 (secondary analysis)</td>
<td>Hydromorphone ER</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Peniston, 2012</td>
<td>Oxymorphone ER</td>
<td>Patients with low back pain taking SSRIs or SNRIs</td>
</tr>
<tr>
<td>Schwartz, 2011</td>
<td>Tapentadol ER</td>
<td>Painful diabetic neuropathy</td>
</tr>
<tr>
<td>Steiner, 2011b</td>
<td>Buprenorphine transdermal system</td>
<td>Opioid-naive patients with low back pain</td>
</tr>
<tr>
<td>Yarlas, 2013</td>
<td>Buprenorphine transdermal system</td>
<td>Opioid-naive patients with chronic low back pain</td>
</tr>
</tbody>
</table>

### Summary and Recommendation

A streamlined report on this topic based on direct and indirect evidence would likely be a medium update based on head to head, active control (long acting versus short acting), and placebo controlled studies of included interventions. The EPC recommends limiting the report to head to head and active comparisons (i.e. long-acting versus short-acting formulations) resulting in a small size report. If work on a small report started in Feb 2014, the final report would be delivered in July 2014. Two states have currently scheduled to review this class before July 2014 (February and May); we have no other PDL meeting scheduling information for this class.
Appendix A. Comparative Effectiveness Reviews

Noninvasive Treatments for Low Back Pain (EPC report in progress)

Question 1 What are the comparative benefits and harms of different pharmacological therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis? (Including NSAIDs, acetaminophen, opioids, muscle relaxants, antiseizure medications, antidepressants, corticosteroids and topicals/patch-delivered medications)

Question 2 What are the comparative benefits and harms of different nonpharmacological, noninvasive therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis? (Including but not limited to interdisciplinary rehabilitation, exercise (various types), physical modalities (ultrasound, Transcutaneous Electrical Nerve Stimulation (TENS), Electrical Muscle Stimulation (EMS), Interferential Therapy (IFT), heat (various forms), ice), traction tables/devices, back supports/bracing, spinal manipulation, various psychological therapies, acupuncture, massage therapy (various types), yoga, magnets and low level lasers)

The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain (EPC Report in progress)

Effectiveness and comparative effectiveness

1. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?

2. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance abuse and related disorders, mental health disorder and those at high risk for addiction and medical comorbidities)?

3. In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid therapies (pharmacological or non-pharmacological) on outcomes related to pain, function, and quality of life?

4. In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (pharmacological or non-pharmacological) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Evaluation of Opioid Use for Patients with Chronic Non-Cancer Pain: Clinical Evidence (CADTH)

RESEARCH QUESTION
What is the clinical evidence evaluating inappropriate use of opioids by patients with chronic non-cancer pain, using administrative databases?

KEY MESSAGE
Seven non-randomized studies using administrative databases to evaluate inappropriate use of opioids by patients with chronic non-cancer pain were identified.

METHODS
A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and May 29, 2012. Internet links were provided, where available.

RESULTS
Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies. Seven non-randomized studies using administrative databases to evaluate inappropriate use of opioids by patients with chronic non-cancer pain were identified. No relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials were identified.

Long-acting Opioids for Chronic Pain: Comparative Efficacy and Safety (CADTH)

RESEARCH QUESTIONS
1. What is the comparative efficacy of different long-acting opioids for adult patients with chronic non-cancer pain?

2. What is the comparative safety of different long-acting opioids for adult patients with chronic non-cancer pain?

KEY MESSAGE
Evidence suggests that the comparative efficacy and safety of different long-acting opioids for adult patients with chronic non-cancer pain is generally similar.

METHODS
A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and October 24, 2011. Internet links were provided, where available.

RESULTS
Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.
Fifteen randomized controlled trials and 11 non-randomized studies were identified regarding the comparative efficacy and safety of different long-acting opioids for adult patients with chronic non-cancer pain. No health technology assessment reports, systematic reviews, or meta-analyses were identified. Additional studies of potential interest are provided in the appendix.


CONTEXT AND POLICY ISSUES
Opioids are indicated as part of a comprehensive plan for the management of chronic pain in carefully selected and monitored patients. A marked increase in the misuse, abuse, and diversion of prescription opioids, however, has become a societal and public health concern and has led to increased healthcare costs and alterations in treatment plans. Non-medical use of prescription opioids is a public health concern because it has been linked to serious personal health consequences, including addiction, fatal opioid overdose, injection drug use and polydrug use. Opioid diversion signifies any instance where drugs are re-routed from their lawful purpose at any point in the pharmaceutical manufacturing and distribution process. For example, opioids can be diverted in the preclinical stages through theft at plants, in transit or at pharmacies. Opioids can also be diverted during the post-clinical phase by sharing, selling and misusing of prescribed medications or by stealing medications. Opioid misuse can be defined as the use of opioids for a medical purpose, other than as directed or indicated, whether or not intentional and regardless of harm. Substance abuse can be defined as the use of any substance when such use is unlawful, or when such use is detrimental to the user or others. The distinctions between these terms are often blurred and within the literature there has been no consensus around the definitions of opioid diversion, opioid misuse and substance abuse. In Canada, the prescribing of opioids has increased dramatically in recent years. For example, oxycodone prescriptions among Ontario Drug Benefit recipients rose from 1991 to 2007, from 23 prescriptions per 1000 individuals per year to 197 prescriptions per 1000 individuals per year. These increases have been accompanied by increases in opioid-related harms such as addiction and overdose. Of the 1095 people who died of opioid-related overdose in Ontario, during 1991 to 2007, 56% had been given opioid prescriptions within four weeks before death. The purpose of this report is to review the clinical evidence regarding opioid management practices to reduce drug diversion and misuse; examine the evidence-based guidelines for opioid management practices to reduce opioid diversion and misuse; and examine the clinical evidence regarding opioid use or prescription patterns for the prediction of substance abuse.

Opioids compared to placebo or other treatments for chronic low-back pain.
Abstract
BACKGROUND:
The use of opioids in the long-term management of chronic low-back pain (CLBP) has increased dramatically. Despite this trend, the benefits and risks of these medications remain unclear. This review is an update of a Cochrane review first published in 2007.
OBJECTIVES:
To determine the efficacy of opioids in adults with CLBP.
SEARCH METHODS:
We electronically searched the Cochrane Back Review Group's Specialized Register, CENTRAL, CINAHL and PsycINFO, MEDLINE, and EMBASE from January 2006 to October 2012. We checked the reference lists of these trials and other relevant systematic reviews for potential trials for inclusion.

SELECTION CRITERIA:
We included randomized controlled trials (RCTs) that assessed the use of opioids (as monotherapy or in combination with other therapies) in adults with CLBP that were at least four weeks in duration. We included trials that compared non-injectable opioids to placebo or other treatments. We excluded trials that compared different opioids only.

DATA COLLECTION AND ANALYSIS:
Two authors independently assessed the risk of bias and extracted data onto a pre-designed form. We pooled results using Review Manager (RevMan) 5.2. We reported on pain and function outcomes using standardized mean difference (SMD) or risk ratios with 95% confidence intervals (95% CI). We used absolute risk difference (RD) with 95% CI to report adverse effects.

MAIN RESULTS:
We included 15 trials (5540 participants). Tramadol was examined in five trials (1378 participants); it was found to be better than placebo for pain (SMD -0.55, 95% CI -0.66 to -0.44; low quality evidence) and function (SMD -0.18, 95% CI -0.29 to -0.07; moderate quality evidence). Transdermal buprenorphine (two trials, 653 participants) may make little difference for pain (SMD -2.47, 95%CI -2.69 to -2.25; very low quality evidence), but no difference compared to placebo for function (SMD -0.14, 95%CI -0.53 to 0.25; very low quality evidence). Strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol), examined in six trials (1887 participants), were better than placebo for pain (SMD -0.43, 95%CI -0.52 to -0.33; moderate quality evidence) and function (SMD -0.26, 95% CI -0.37 to -0.15; moderate quality evidence). One trial (1583 participants) demonstrated that tramadol may make little difference compared to celecoxib (RR 0.82, 95% CI 0.76 to 0.90; very low quality evidence) for pain relief. Two trials (272 participants) found no difference between opioids and antidepressants for either pain (SMD 0.21, 95% CI -0.03 to 0.45; very low quality evidence), or function (SMD -0.11, 95% -0.63 to 0.42; very low quality evidence). The included trials in this review had high drop-out rates, were of short duration, and had limited interpretability of functional improvement. They did not report any serious adverse effects, risks (addiction or overdose), or complications (sleep apnea, opioid-induced hyperalgesia, hypogonadism). In general, the effect sizes were medium for pain and small for function.

AUTHORS' CONCLUSIONS:
There is some evidence (very low to moderate quality) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks. There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP.
Opioids for neuropathic pain.
McNicol ED, Midbari A, Eisenberg E.

Abstract

BACKGROUND:
This is an updated version of the original Cochrane review published in Issue 3, 2006, which included 23 trials. The use of opioids for neuropathic pain remains controversial. Studies have been small, have yielded equivocal results, and have not established the long-term profile of benefits and risks for people with neuropathic pain.

OBJECTIVES:
To reassess the efficacy and safety of opioid agonists for the treatment of neuropathic pain.

SEARCH METHODS:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (to 24th October 2012), MEDLINE (1966 to 24th October 2012 ), and EMBASE (1980 to 24th October 2012) for articles in any language, and reference lists of reviews and retrieved articles.

SELECTION CRITERIA:
We included randomized controlled trials (RCTs) in which opioid agonists were given to treat central or peripheral neuropathic pain of any etiology. Pain was assessed using validated instruments, and adverse events were reported. We excluded studies in which drugs other than opioid agonists were combined with opioids or opioids were administered epidurally or intrathecally.

DATA COLLECTION AND ANALYSIS:
Two review authors independently extracted data and included demographic variables, diagnoses, interventions, efficacy, and adverse effects.

MAIN RESULTS:
Thirty-one trials met our inclusion criteria, studying 10 different opioids: 23 studies from the original 2006 review and eight additional studies from this updated review. Seventeen studies (392 participants with neuropathic pain, average 22 participants per study) provided efficacy data for acute exposure to opioids over less than 24 hours. Sixteen reported pain outcomes, with contradictory results; 8/16 reported less pain with opioids than placebo, 2/16 reported that some but not all participants benefited, 5/16 reported no difference, and 1/16 reported equivocal results. Six studies with about 170 participants indicated that mean pain scores with opioid were about 15/100 points less than placebo. Fourteen studies (845 participants, average 60 participants per study) were of intermediate duration lasting 12 weeks or less; most studies lasted less than six weeks. Most studies used imputation methods for participant withdrawal known to be associated with considerable bias; none used a method known not to be associated with bias. The evidence, therefore, derives from studies predominantly with features likely to overestimate treatment effects, i.e. small size, short duration, and potentially inadequate handling of dropouts. All demonstrated opioid efficacy for spontaneous neuropathic pain. Meta-analysis demonstrated at least 33% pain relief in 57% of participants receiving an opioid versus 34% of those receiving placebo. The overall point estimate of risk difference was 0.25 (95% confidence interval (CI) 0.13 to 0.37, P < 0.0001), translating to a number needed to treat for an additional beneficial
outcome (NNTB) of 4.0 (95% CI 2.7 to 7.7). When the number of participants achieving at least 50% pain relief was analyzed, the overall point estimate of risk difference between opioids (47%) and placebo (30%) was 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0). In the updated review, opioids did not demonstrate improvement in many aspects of emotional or physical functioning, as measured by various validated questionnaires. Constipation was the most common adverse event (34% opioid versus 9% placebo: number needed to treat for an additional harmful outcome (NNTH) 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0). More participants withdrew from opioid treatment due to adverse events (13%) than from placebo (4%) (NNTH 4.0; 95% CI 3.0 to 5.6). Conversely, more participants receiving placebo withdrew due to lack of efficacy (12%) versus (2%) receiving opioids (NNTH -11.1; 95% CI -20.0 to -8.3).

AUTHORS' CONCLUSIONS:

Since the last version of this review, new studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions. Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.

Methadone for chronic non-cancer pain in adults.
Haroutiunian S, McNicol ED, Lipman AG.

Author information

Abstract

BACKGROUND:
Methadone belongs to a class of analgesics known as opioids, that are considered the cornerstone of therapy for moderate-to-severe pain due to life-threatening illnesses; however, their use in chronic non-cancer pain (CNCP) is controversial. Methadone has many characteristics that differentiate it from other opioids, which suggests that it may have a different efficacy and safety profile.

OBJECTIVES:
To assess the analgesic effectiveness and safety of methadone in the treatment of CNCP.

SEARCH METHODS:
We identified both randomized controlled trials (RCTs) and non-randomized studies of methadone use in chronic pain by searching the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library 2011, issue 11, MEDLINE (1950 to November 2011),
and EMBASE (1980 to November 2011), together with reference lists of retrieved papers and reviews.

**SELECTION CRITERIA:**
We included RCTs with pain assessment as either the primary or secondary outcome. Quasi-randomized studies, cohorts and case-control trials were also considered for inclusion because we suspected that the beneficial and harmful effects of methadone in CNCP may not be adequately addressed in RCTs.

**DATA COLLECTION AND ANALYSIS:**
Two review authors independently extracted efficacy and adverse event data and assessed risk of bias.

**MAIN RESULTS:**
We included two RCTs and one non-randomized study, involving a total of 181 participants. Both RCTs were cross-over studies, one involving 19 participants with diverse neuropathic pain syndromes, the other involving 76 participants with postherpetic neuralgia. Study phases were 20 days and approximately eight weeks, respectively. The non-randomized study retrospectively evaluated 86 outpatients over an average of 8.8 ± 6.3 months. One RCT reported average pain intensity and pain relief, and found statistically significant improvements versus placebo for both outcomes, with 10 mg and 20 mg daily doses of methadone. The second RCT reported differences in pain reduction between methadone and morphine and found morphine to be statistically superior. The non-randomized study found that in patients initially prescribed methadone it was effective in fewer participants than in those initially prescribed other long-acting opioids (28% versus 42%, 33% and 50% for morphine, oxycodone and transdermal fentanyl, respectively). One RCT compared incidences for several individual adverse events, but found a difference between methadone and placebo for only one event, dizziness (P = 0.041).

**AUTHORS' CONCLUSIONS:**
The three studies provide very limited evidence of the efficacy of methadone for CNCP, and there were too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies. No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments.
Appendix B. Abstracts of potentially relevant new trials of long-acting opioids (Scan 2)

Head-to-head trials (N=2)

OBJECTIVE: Buprenorphine and fentanyl transdermal patches are used widely for the management of persistent malignant and nonmalignant pain. Buprenorphine and fentanyl transdermal patches, both potent opioids, are considered to be equally efficacious in managing persistent pain. Various retrospective studies comparing dosage changes of buprenorphine and fentanyl patches in persistent pain patients have been completed; however, no long-term prospective, randomized, clinical study has compared the effectiveness of these patches. The objective of the present study was to satisfy this need.

AIMS: This study aims to compare prospectively the long-term efficacy, acceptability, and side effects of both of these patches in patients with persistent pain. This study would examine the feasibility and lay the groundwork for a larger, multicenter study where such efficacy and safety outcomes of the two medications can be adequately assessed.

DESIGN: The participants were 46 adults (range 22-80 years.) with nonmalignant persistent pain (mean=11 years), predominantly with lower back pain. Data were obtained monthly for 12 months. Participants recruited were opioid-naive patients, having pain for the greater part of the day and night, and appropriate for treatment with transdermal patches. After initial assessment, participants were randomly allocated to either buprenorphine or fentanyl patch treatment. Participants were then titrated to optimal doses of medication. Patients with adverse effects or unsatisfactory pain relief were treated alternatively and discontinued from the study.

RESULTS: Nearly one-third of all patients, 41% (8 of 22) of the transdermal buprenorphine (TDB) group and 37.5% (8 of 24) of the transdermal fentanyl (TDF) group stopped treatment due to unacceptable side effects or inadequate pain relief. The remaining participants showed a similar trend in the improvement of pain intensity, physical activity, sleep, and mood throughout the study. Significant relief in the intensity of pain was achieved for the initial 6 months and the effects stabilized in the remainder of the study in both groups. There were no significant group differences over time. However, a higher equipotent dose of fentanyl was required for comparable pain relief. Compared with TDF group, the TDB group initially experienced relatively less side effects. However, a greater number of buprenorphine users suffered from local skin reactions. Buprenorphine users had significant improvement in mood. Thirty-one percent (5 of 16) of the buprenorphine group and 57% (8 of 14) of the fentanyl users needed additional pain relief medications by the end of 3 months. By the end of 12 months, a significant number 78% (7 of 9) of buprenorphine users but comparatively fewer 44% (4 of 9) of the fentanyl group used rescue medicines. Both had more doctor visits in the latter half of the study.

CONCLUSION: Thirty percent of the total number of patients discontinued treatment because of side effects or unsatisfactory pain relief. For those continuing treatment, clinical improvements were seen in the initial 6 months in both groups. Fifty percent of the TDB and 43% of TDF groups had significant relief in 3 months, which persisted up to 6
months. Only 11% and 13% of patients, respectively, had sustained relief after 6 months. Twenty percent more patients in the TDB group benefited significantly in symptoms of depression from TDB compared with the TDF group. Interestingly, switching of patches seemed to increase acceptability by preventing adverse effects and tolerance. Confirmation of these effects should be studied in future with a multicenter study and larger sample. Wiley Periodicals, Inc.


Once-daily hydromorphone extended-release (OROS) hydromorphone ER and oxycodone controlled-release (CR) are semisynthetic, ER opioid analgesics with established efficacy. An open-label, randomized, 24-week, parallel group, flexible-dose study demonstrated noninferiority of OROS hydromorphone ER vs. twice-daily oxycodone CR in patients with chronic noncancer pain. In total, 112 patients were enrolled in a 28-week, open-label extension study; 60 patients received OROS hydromorphone ER and 52 received oxycodone CR. The primary efficacy measure was the change from baseline to Weeks 38 and 52 in Brief Pain Inventory item "pain right now." Global assessments of efficacy, dosing convenience, and tolerability were secondary endpoints. Mean change in "pain right now" from baseline to Week 38 was -3.0 (OROS hydromorphone ER) vs. -2.8 (oxycodone CR), and from baseline to Week 52 was -2.9 vs. -2.8; these changes were similar to the changes in the core phase (-2.1 vs. -2.1). Similar improvements were demonstrated for secondary assessments, including pain, pain interference, and quality of life. At Week 52, global assessment of efficacy was rated as "very good" or "good" by the majority of patients (OROS hydromorphone ER, 91.7%; oxycodone CR, 86.5%). More patients in the OROS hydromorphone ER group (35.0% vs. 21.2%) assessed mode of drug intake as "very convenient." The majority of patients receiving OROS hydromorphone ER (88.3%) and oxycodone CR (88.5%) rated tolerability as "good" or "very good" at Week 52; few patients discontinued treatment because of an adverse event (1.6% vs. 0.4%, respectively). The effectiveness of OROS hydromorphone ER and oxycodone CR was maintained through 1 year. 2012 Janssen Global Services. Pain Practice 2012 World Institute of Pain.

Placebo controlled trials (N=3)

OBJECTIVES: Patients with chronic noncancer pain frequently report symptoms of depression and anxiety (negative affect), which are associated with higher ratings of pain intensity and a greater likelihood of being prescribed chronic opioid therapy. The purpose of this secondary analysis was to test the hypothesis that initial levels of negative affect can predict treatment-related outcomes in a double-blind, placebo-controlled study of extended-release (ER) hydromorphone among opioid-tolerant patients with chronic low back pain.
METHODS: Four hundred fifty-nine (N = 459) patients participated in the titration/conversion phase of a multicenter study, of which 268 were randomized to receive once-daily hydromorphone or placebo. All patients completed the Hospital Anxiety and Depression Scale (HADS) at baseline and were divided evenly into Low (N = 157), Moderate (N = 155), and High (N = 147) negative affect groups based on their scores. Group differences in numerical pain intensity measures at home and in the clinic, Roland-Morris Disability ratings, and measures of symptoms from the Subjective Opiate Withdrawal Scale (SOWS) throughout the trial were analyzed.

RESULTS: Two hundred sixty-eight of the initial 459 subjects who entered the 2 to 4-week titration/conversion phase (pretreatment) were successfully randomized to either placebo or ER hydromorphone; a total of 110 patients then completed this double-blind phase of the study. Those in the Moderate and High negative affect groups tended to drop out more often during the titration/conversion phase because of the adverse effects or lack of efficacy of their prescribed opioid than those in the Low negative mood group (P < 0.05). Overall, those patients in the Moderate and High groups reported significantly higher pain intensity scores in at-home and in-clinic pain intensity ratings (P < 0.05), greater disability on the Roland-Morris Scale (P < 0.01), and more withdrawal symptoms on the SOWS (P < 0.05) than those in the Low group. Higher negative affect scores also predicted less favorable ratings of the study drug during the titration phase (P < 0.05). Interestingly, the High negative affect group showed the most improvement in pain in the placebo condition (P < 0.05).

CONCLUSIONS: Negative affect is associated with diminished benefit during a trial of opioid therapy and is predictive of dropout in a controlled clinical trial. 2012 The Authors. Pain Practice 2012 World Institute of Pain.


OBJECTIVE: Opioids are recommended for patients with moderate to severe pain due to osteoarthritis (OA), who do not receive adequate analgesia from nonopioid treatment. The objective of this study was to evaluate the efficacy and safety of OROS hydromorphone extended-release (ER) compared with placebo in patients with moderate to severe pain associated with OA.

METHODS: This was a randomized, placebo-controlled, double-blind, fixed-dose study. Patients received placebo or fixed-dose OROS hydromorphone ER (8 or 16 mg). The primary efficacy measure was pain intensity score (11-point Numeric Rating Scale) at Maintenance Week 12, analyzed with baseline observation carried forward (BOCF) imputation for missing data.

RESULTS: This study did not meet the primary efficacy measure using the BOCF imputation. Study discontinuation was high (52%). When analyzed using last observation carried forward (LOCF) imputation, the prespecified alternate method, OROS hydromorphone ER 16 mg provided significantly better analgesia than placebo (P = 0.0009). Treatment was associated with significant improvements in patient global assessment (P = 0.01), the overall Western Ontario and McMaster Osteoarthritis Index (WOMAC) (P = 0.0003), and its subscales: pain (P = 0.0001), stiffness (P = 0.0023), and physical function (P =}
0.0006). Gastrointestinal adverse events, such as constipation and nausea, were common among patients receiving OROS hydromorphone ER.

CONCLUSIONS: OROS hydromorphone ER failed to achieve statistical significance for the primary endpoint using the prespecified imputation method (BOCF), likely due to the high discontinuation rate associated with the fixed-dose design. When data were analyzed according to an alternate method of imputation (LOCF), OROS hydromorphone ER demonstrated statistically significant improvements in pain, stiffness, and physical function. 2012 The Authors. Pain Practice 2012 World Institute of Pain.


UNLABELLED: This study evaluated the impact of treatment with Buprenorphine Transdermal System (BTDS) on the health-related quality of life for patients with moderate-to-severe chronic low back pain (CLBP), and the correspondence between quality of life and pain. A multicenter, enriched, double-blind (DB), placebo-controlled, randomized trial evaluated BTDS 10 and 20 μg/hour for treatment of opioid-naive patients with moderate-to-severe CLBP. The SF-36v2 survey, which measures 8 domains of quality of life, was administered at screening and following an open-label run-in period with BTDS and at weeks 4, 8, and 12 of the DB phase. Post hoc analyses compared SF-36v2 scores between BTDS and placebo groups during the DB phase. Condition burden was examined through comparisons with a U.S. general population sample. Correlations examined the correspondence between quality of life and pain measures. BTDS produced larger improvements than placebo at 12 weeks in all quality-of-life domains (Ps < .05). Treatment group differences in both physical and mental quality of life emerged by 4 weeks. Patients' pretreatment quality of life was worse than that in the general population (Ps < .05); only BTDS treatment eliminated deficits in pain, social functioning, and role limitations due to emotional health. Improvements in quality of life were moderately associated with pain reduction. These data suggest that moderate-to-severe CLBP patients receiving BTDS exhibited better quality of life than patients receiving placebo.

PERSPECTIVE: This post hoc analysis suggests that patients with moderate-to-severe CLBP treated with BTDS exhibit better health-related quality of life than those using placebo within 4 weeks of treatment, and were more likely to exhibit clinically meaningful improvements in quality of life following 12 weeks of treatment. Copyright 2013 American Pain Society. Published by Elsevier Inc. All rights reserved.

Abstracts of potentially relevant new trials of long-acting opioids (Scan 1)

Head-to-head trials (N=3)
BACKGROUND: Tapentadol is a novel, centrally acting analgesic with mu-opioid receptor agonist and norepinephrine reuptake inhibitor activity. OBJECTIVE: to evaluate the efficacy and safety of Tapentadol extended release (ER) compared with oxycodone controlled release (CR) for management of moderate to severe chronic osteoarthritis-related knee pain. METHODS: this was a randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study during which patients received Tapentadol ER, oxycodone CR or placebo for a 3-week titration period followed by a 12-week maintenance period. The study was carried out at sites in Australia, Canada, New Zealand and the US. A total of 1030 patients with chronic osteoarthritis-related knee pain were randomized to receive Tapentadol ER 100-250 mg twice daily, oxycodone HCl CR 20-50 mg twice daily or placebo. Primary endpoints (as determined prior to initiation of the study) were the changes from baseline in average daily pain intensity (rated by patients on an 11-point numerical rating scale) over the last week of maintenance and over the entire 12-week maintenance period; last observation carried forward was used to impute missing values after early treatment discontinuation. RESULTS: efficacy and safety were evaluated for 1023 patients. Tapentadol ER significantly reduced average pain intensity from baseline to week 12 of the maintenance period versus placebo (least squares mean [LSM] difference [95% CI], -0.7 [-1.04, -0.33]), and throughout the maintenance period (-0.7 [-1.00, -0.33]). Oxycodone CR significantly reduced average pain intensity from baseline throughout the maintenance period versus placebo (LSM difference [95% CI], -0.3 [-0.67, -0.00]) but not at week 12 (-0.3 [-0.68, 0.02]). A significantly higher percentage of patients achieved > or =50% improvement in pain intensity in the Tapentadol ER group (32.0% [110/344]) compared with the placebo group (24.3% [82/337]; p = 0.027), indicating a clinically significant improvement in pain intensity, while a significantly lower percentage of patients achieved > or =50% improvement in pain intensity in the oxycodone CR group (17.3% [59/342]; p = 0.023 vs placebo). In the placebo, Tapentadol ER and oxycodone CR groups, respectively, 61.1% (206/337), 75.9% (261/344) and 87.4% (299/342) of patients reported at least one treatment-emergent adverse event (TEAE); incidences of gastrointestinal-related TEAEs were 26.1% (88/337), 43.0% (148/344) and 67.3% (230/342). CONCLUSION: treatment with Tapentadol ER 100-250 mg twice daily or oxycodone HCl CR 20-50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with Tapentadol ER than with oxycodone CR.


OBJECTIVE: To evaluate the efficacy and safety of tapentadol extended release (ER) for the management of moderate to severe chronic low back pain.

RESEARCH DESIGN: Patients (N = 981) were randomized 1:1:1 to receive tapentadol ER 100 - 250 mg b.i.d., oxycodone HCl controlled release (CR) 20 - 50 mg b.i.d., or placebo over 15 weeks (3-week titration period, 12-week maintenance period).

MAIN OUTCOME MEASURES: Efficacy was assessed as change from baseline in average pain intensity (11-point NRS) at week 12 of the maintenance period and
throughout the maintenance period; last observation carried forward was used to impute missing pain scores. Adverse events (AEs) were monitored throughout the study.

RESULTS: Tapentadol ER significantly reduced average pain intensity versus placebo at week 12 (least squares mean difference vs placebo [95% confidence interval], -0.8 [-1.22, -0.47]; p < 0.001) and throughout the maintenance period (-0.7 [-1.06, -0.35]; p < 0.001). Oxycodone CR significantly reduced average pain intensity versus placebo at week 12 (-0.9 [-1.24, -0.49]; p < 0.001) and throughout the maintenance period (-0.8 [-1.16, -0.46]; p < 0.001). Tapentadol ER was associated with a lower incidence of treatment-emergent AEs (TEAEs) than oxycodone CR. Gastrointestinal TEAEs, including constipation, nausea, and vomiting, were among the most commonly reported TEAEs (placebo, 26.3%; tapentadol ER, 43.7%; oxycodone CR, 61.9%). The odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower with tapentadol ER than with oxycodone CR (both p < 0.001).

CONCLUSIONS: Tapentadol ER (100 - 250 mg b.i.d.) effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone HCl CR (20 - 50 mg b.i.d.).


BACKGROUND: Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action: -opioid receptor agonism and norepinephrine reuptake inhibition. This randomized, open-label phase 3 study (ClinicalTrials.gov Identifier: NCT00361504) assessed the long-term safety and tolerability of tapentadol extended release (ER) in patients with chronic knee or hip osteoarthritis pain or low back pain.

METHODS: Patients were randomized 4:1 to receive controlled, adjustable, oral, twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg) for up to 1 year. Efficacy evaluations included assessments at each study visit of average pain intensity (11-point numerical rating scale) over the preceding 24 hours. Treatment-emergent adverse events (TEAEs) and discontinuations were monitored throughout the study.

RESULTS: A total of 1,117 patients received at least 1 dose of study drug. Mean (standard error) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11) at baseline and decreased to 4.4 (0.09) and 4.5 (0.17) at endpoint. The overall incidence of TEAEs was 85.7% in the tapentadol ER group and 90.6% in the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, TEAEs led to discontinuation in 22.1% and 36.8% of patients; gastrointestinal TEAEs led to discontinuation in 8.6% and 21.5% of patients.

CONCLUSION: Tapentadol ER (100 to 250 mg bid) was associated with better gastrointestinal tolerability than oxycodone HCl CR (20 to 50 mg bid) and provided sustainable relief of moderate to severe chronic knee or hip osteoarthritis or low back pain for up to 1 year. 2010 World Institute of Pain.

Active-control trials (N=3)

Dose selection of a once-daily, osmotic-controlled extended-release (ER) hydromorphone assumes that this drug and immediate-release (IR) hydromorphone are dose equivalent. This trial evaluated dose equivalence using a measure of assay sensitivity. Patients were converted to open-label IR hydromorphone, underwent dose titration, and those on a satisfactory dose entered a randomized, double-blind phase receiving 7 days of: 1) hydromorphone IR 5 times/day at approximately this dose; 2) once-daily hydromorphone ER at this dose; or 3) once-daily hydromorphone ER at one-half this dose. Efficacy was measured using breakthrough medication use, pain, sleep, and global assessments. Of 148 patients, 113 (76%) were randomized. IR and full-dose ER groups produced comparable effects on all measures. Although the prespecified primary analysis of the difference in total daily dose of breakthrough medication between the full-dose ER and half-dose ER groups was not significant, more patients in the half-dose ER group required an increase in breakthrough medication (P = .026) and the half-dose ER group both increased the number of breakthrough doses (P = .026) and had greater percent change in the total daily dose of breakthrough medication (P = .037) than the full-dose group, suggesting that switching from IR to ER hydromorphone at the same daily dose provides equivalent analgesia. PERSPECTIVE: In a randomized, double-blind trial, the same total daily dose of immediate-release hydromorphone and once-daily osmotic-controlled extended-release hydromorphone had comparable effects. Detection of different effects between blinded dose levels was used as a measure of assay sensitivity. The measure of assay sensitivity can enhance the interpretation of dose equivalence or noninferiority trials. Copyright 2012 American Pain Society. Published by Elsevier Inc. All rights reserved.


BACKGROUND: Tapentadol, a novel, centrally acting analgesic with 2 mechanisms of action (mu-opioid receptor agonism and norepinephrine reuptake inhibition), has been developed in an immediate-release (IR) and an extended-release (ER) formulation. Determination of the safety and equianalgesic ratios for conversion between formulations is important for physicians with patients taking tapentadol IR who may want to switch to tapentadol ER, or vice versa, for any reason.

OBJECTIVES: To test whether the total daily dose (TDD) of tapentadol IR may be directly converted into a comparable TDD of tapentadol ER, and vice versa, with equivalent efficacy and comparable safety.

STUDY DESIGN: Randomized, double-blind, 2-period (2 weeks each) crossover study.

SETTING: Study centers (N = 13) in the United States.

METHODS: Patients with moderate to severe chronic low back pain received tapentadol IR 50, 75, or 100 mg every 4 or 6 hours (maximum TDD, 500 mg) during the 3-week open-label period to identify an optimal, stable dose of tapentadol IR for each patient. Patients were then randomized in a 1:1 ratio to receive, during the first 2-week double-blind period, either the optimal dose of tapentadol IR identified during the open-label period or a TDD of tapentadol ER (100, 150, 200, or 250 mg bid) that was as close as possible to the TDD of tapentadol IR from the open-label period. During a subsequent, 2-
week double-blind period, patients received whichever formulation was not received during the first double-blind period. The primary endpoint was the mean average daily pain intensity (on an 11-point numerical rating scale) during the last 3 days of each double-blind treatment period. If the 95% confidence intervals (CIs) of the least squares mean difference between formulations were within the range of -2 to 2, the formulations were considered equivalent.

RESULTS: Of the 88 patients who were randomized, 72 completed both double-blind treatments, and 60 were included in the per-protocol analysis. The mean (standard deviation [SD]) pain intensity score decreased from 7.3 (1.19) pre-treatment to 4.2 (2.13) after 3 weeks of open-label treatment with tapentadol IR and remained constant throughout double-blind treatment (3.9 or 4.0 each week) for both formulations. The mean (SD) of the average pain intensity scores over the last 3 days of double-blind treatment was 3.9 (2.17) with tapentadol IR and 4.0 (2.29) with tapentadol ER, for an estimated difference of 0.1 (95% CI, -0.09 to 0.28). For both tapentadol IR and tapentadol ER, the median TDD administered was 300.0 mg, and acetaminophen was used by 39.5% and 45.2% of patients, respectively. The incidence of treatment-emergent adverse events during double-blind treatment was similar between the tapentadol IR and tapentadol ER groups.

LIMITATIONS: Use of rescue medication theoretically could have influenced pain measurements, but in practice, pain measurements did not differ between treatments.

CONCLUSIONS: Approximately equivalent TDDs of tapentadol IR and tapentadol ER provided equivalent analgesic efficacy for the relief of moderate to severe chronic low back pain and were similarly well tolerated, allowing for direct conversion between the 2 formulations. Clinical Trial Registration: NCT00594516.


In this enriched design study, 1,160 opioid-experienced patients with chronic, moderate to severe low back pain entered an open-label run-in period; 660 demonstrated analgesic benefit from and tolerability to buprenorphine transdermal system 20 mcg/hour (BTDS 20) treatment and were randomized to receive either BTDS 20, BTDS 5 mcg/hour (BTDS 5), or the active control (immediate release oxycodone 40-mg/day) during an 84-day double-blind phase. The primary endpoint, "average pain in the last 24 hours" during double-blind weeks 4, 8, and 12, was significantly lower for patients receiving BTDS 20 compared with patients receiving BTDS 5 (P < .001, treatment difference of -.67). A treatment difference of -.75 in favor of oxycodone 40 mg/day versus BTDS 5 (P < .001) indicated the assay sensitivity of the study. Four sensitivity analyses, secondary, and exploratory analyses supported the results of the primary analysis. Incidences of treatment-emergent adverse events were 56% during the open-label period, and 59, 77, and 73% for the BTDS 5, BTDS 20, and oxycodone 40 mg/day treatment groups, respectively, during the double-blind phase. One death considered unrelated to study treatment occurred in a patient receiving BTDS 10 during the run-in period. BTDS 20 treatment was demonstrated to be efficacious and generally well tolerated.

PERSPECTIVE: This article presents results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch.
containing the opioid buprenorphine (BTDS). In this active controlled, superiority study with an enriched design, BTDS 20 was found to be efficacious and generally well tolerated. Copyright A 2011 American Pain Society. Published by Elsevier Inc. All rights reserved.

**Placebo controlled trials (N=4)**


Although often successful in acute settings, long-term use of opioid pain medications may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to attain pain relief.

Analgesic tolerance, and more recently opioid-induced hyperalgesia, have been invoked to explain such declines in opioid effectiveness over time. Because both phenomena result in inadequate analgesia, they are difficult to distinguish in a clinical setting.

Patients with otherwise uncomplicated low-back pain were titrated to comfort or dose-limiting side effects in a prospective, randomized, double-blind, placebo-controlled clinical trial using sustained-release morphine or weight-matched placebo capsules for 1 month. A total of 103 patients completed the study, with an average end titration dose of 78 mg morphine/d. After 1 month, the morphine-treated patients developed tolerance to the analgesic effects of remifentanil, but did not develop opioid-induced hyperalgesia. On average, these patients experienced a 42% reduction in analgesic potency. The morphine-treated patients experienced clinically relevant improvements in pain relief, as shown by a 44% reduction in average visual analogue scale pain levels and a 31% improvement in functional ability. The differences in visual analogue scale pain levels (P = .003) and self-reported disability (P = .03) between both treatment groups were statistically significant.

After 1 month of oral morphine therapy, patients with chronic low-back pain developed tolerance but not opioid-induced hyperalgesia. Improvements in pain and functional ability were observed. Copyright 2012 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.


**BACKGROUND:** Opioids and antidepressants are frequently prescribed for chronic low back pain (cLBP). This post hoc analysis was conducted to assess the tolerability of oxymorphone extended release (ER) for cLBP in patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) compared with patients not taking SSRIs/SNRIs.

**METHODS:** Patients in 2 clinical trials (NCT00225797, November 22, 2004 to July 18, 2005; NCT00226421, October 13, 2004 to August 19, 2005) aged >= 18 years with moderate to severe cLBP were titrated to a stabilized dose of oxymorphone ER during an open-label titration phase and then randomized to treatment with this dose or placebo every 12 hours for 12 weeks. In a post hoc analysis, adverse events (AEs) were compared between patients taking versus not taking SSRIs/SNRIs. Treatment efficacy was assessed as change from baseline in average daily pain intensity on a 100-mm visual analog scale.
RESULTS: Of 575 patients enrolled, 45 of 89 (50.6%) taking SSRIs/SNRIs and 303 of 486 (62.3%) not taking SSRIs/SNRIs successfully titrated to oxymorphone ER. The frequency of any AE did not differ significantly between the 2 subpopulations. During the titration phase, serious AEs occurred more frequently in patients taking SSRIs/SNRIs (3/89; 3.4%) compared with those not taking SSRIs/SNRIs (4/486; 0.8%; \( P = 0.04 \)); however, during the double-blind treatment phase, there was no significant difference in the frequency of serious AEs in patients treated with oxymorphone ER taking (1/29; 3.4%) versus those not taking (3/146; 2.0%) SSRIs/SNRIs. Visual analog scale scores were similar in patients taking versus those not taking SSRIs/SNRIs throughout the study.

CONCLUSION: The concomitant use of oxymorphone ER with SSRIs or SNRIs was well tolerated in patients with cLBP.


OBJECTIVE: Painful diabetic peripheral neuropathy (DPN) may not be adequately managed with available therapeutic options. This phase III, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol extended release (ER) for relieving painful DPN.

RESEARCH DESIGN AND METHODS: Patients (n=588) with at least a 3-month history of opioid and/or non-opioid analgesic use for DPN, dissatisfaction with current treatment, and an average pain intensity score of at least 5 on an 11-point numerical rating scale (NRS; 0='no pain,' 10='pain as bad as you can imagine') were titrated to an optimal dose of tapentadol ER (100-250mg bid) during a 3-week open-label phase. Subsequently, patients (n=395) with at least a 1-point reduction in pain intensity were randomized 1:1 to receive placebo or the optimal fixed dose of tapentadol ER determined during the open-label phase for a 12-week double-blind phase. Clinical trial registration: NCT00455520.

MAIN OUTCOME MEASURES: The primary efficacy outcome was the change in average pain intensity from randomization, determined by twice-daily NRS measurements. Safety was assessed throughout the study. Results: The least-squares mean difference between groups in the change in average pain intensity from the start of double-blind treatment to week 12 was -1.3 (95% confidence interval, -1.70 to -0.92; \( p<0.001 \), tapentadol ER vs. placebo). A total of 60.5% (356/588) of patients reported at least a 30% improvement in pain intensity from the start to the end of the open-label titration phase; of the patients who were randomized to tapentadol ER, 53.6% (105/196) reported at least a 30% improvement from pre-titration to week 12 of the double-blind phase. The most common treatment-emergent adverse events that occurred during double-blind treatment with tapentadol ER included nausea, anxiety, diarrhea, and dizziness. Potential limitations of this study are related to the enriched enrollment randomized-withdrawal trial design, which may result in a more homogeneous patient population during double-blind treatment and may present a risk of unblinding because of changes in side effects from the open-label to the double-blind phase.
CONCLUSIONS: Compared with placebo, tapentadol ER 100-250mg bid provided a statistically significant difference in the maintenance of a clinically important improvement in pain 1, 2 and was well-tolerated by patients with painful DPN.


CONTEXT: This article presents the results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch containing the opioid buprenorphine. In this randomized, placebo-controlled study with an enriched enrollment design, the buprenorphine transdermal system (BTDS) was found to be efficacious and generally well tolerated.

OBJECTIVES: This enriched, multicenter, randomized, double-blind study evaluated the efficacy, tolerability, and safety of BTDS in opioid-naive patients who had moderate to severe chronic low back pain.

METHODS: Patients who tolerated and responded to BTDS (10 or 20 mcg/hour) during an open-label run-in period were randomized to continue BTDS 10 or 20 mcg/hour or receive matching placebo. The primary outcome was "average pain over the last 24 hours" at the end of the 12-week double-blind phase, collected on an 11-point scale (0=no pain, 10=pain as bad as you can imagine). Sleep disturbance (Medical Outcomes Study subscale) and total number of supplemental analgesic tablets used were secondary efficacy variables.

RESULTS: Fifty-three percent of patients receiving open-label BTDS (541 of 1024) were randomized to receive BTDS (n=257) or placebo (n=284). Patients receiving BTDS reported statistically significantly lower pain scores at Week 12 compared with placebo (least square mean treatment difference: -0.58, P=0.010). Sensitivity analyses of the primary efficacy variable and results of the analysis of secondary efficacy variables supported the efficacy of BTDS relative to placebo. During the double-blind phase, the incidence of treatment-emergent adverse events was 55% for the BTDS treatment group and 52% for the placebo treatment group. Laboratory, vital sign, and electrocardiogram evaluations did not reveal unanticipated safety findings.

CONCLUSION: BTDS was efficacious in the treatment of opioid-naive patients with moderate to severe chronic low back pain. Most treatment-emergent adverse events observed were consistent with those associated with the use of opioid agonists and transdermal patches. Copyright 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.
Month/Year of Review: March 2014
PDL Classes: Proton Pump Inhibitors

Date of Last Review: November 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- **Preferred Agents**: OMEPRAZOLE CAPSULE DR, PANTOPRAZOLE SODIUM TABLET DR
- **Non-preferred Agents**: Lansoprazole, Dexlansoprazole (DEXILANT®), Rabeprazole (ACIPHEX®), Esomeprazole (NEXIUM®), Omeprazole/Sodium Bicarbonate (ZEGRID®)

Previous Conclusions Recommendations:
- Patients should be re-evaluated for benefits and risks while on long term PPI therapy for potential adverse events.
- There is no consistent difference in efficacy or safety between agents to justify selection of any PPI as clinically superior to the other drugs in the class.
- No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.

PA Criteria: Prior Authorization (PA) criteria is in place for PPIs to promote PDL options, restrict chronic use to patients who failed H2-Antagonists, preferred PPIs or who have severe disease and restricts BID use to patients with severe disease, H. pylori, or pediatric patients (Appendix 1).

Research Questions:
- Is there any new comparative evidence of different PPIs?
- Is there any new comparative safety data of PPIs?
- Are there subpopulations of patients for which one medication or formulation is more effective or associated with fewer adverse effects?

Methods:
The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.¹

Conclusions and Recommendations:
- No further review or research needed at this time; update PA criteria.
- Evaluate comparative costs in executive session.

References:
Appendix 1: PA Criteria:

Proton Pump Inhibitors (PPIs)

Goal(s):
- Promote PDL options.
- Restrict chronic use (greater than eight weeks) to patients who failed H2-antagonist, preferred PPIs or who have severe disease, e.g. Barrett's, or Zollinger Ellison syndrome.
- Restrict BID use to patients with severe disease, H.pylori or pediatric patients.

Notes:
- This is a “global” PA.
- If an active PA for a PPI already exists, then any PPI will pay.
- A new PA is required if the dosing schedule changes, e.g., an active PA for once daily dosing restricts the PPI to once a day.
- BID dosing requires a new PA, however, the strength of the dose could be increased without an additional PA, e.g., a change from 20mg daily could be increased to 40 mg ONCE a day without an additional PA.

Length of Authorization: 2 weeks to lifetime (criteria specific)

Requires PA:
- Non-preferred drugs

Covered Alternatives
- Preferred alternatives listed at www.orpdl.org
- Individual components for treatment of H.pylori that are preferred products.

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>HICL</th>
<th>BRAND</th>
<th>GENERIC</th>
<th>FORMULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL</td>
<td>021607</td>
<td>Nexium</td>
<td>esomeprazole</td>
<td>Capsules, delayed-release: 20, 40mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suspension, delayed-release pkts: 10, 20, 40mg</td>
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<tr>
<td>ORAL</td>
<td>008993</td>
<td>Prevacid</td>
<td>lansoprazole</td>
<td>Capsules, delayed-release: 15, 30 mg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enteric coated granules for oral suspension, delayed release: 15, 30mg</td>
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<tr>
<td>ORAL</td>
<td>025742</td>
<td>Prevacid +</td>
<td>lansoprazole + n</td>
<td>Delayed release capsules + naproxen tablets kit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NapraPAC</td>
<td>naproxen</td>
<td>- 15 – 375, 15 -500</td>
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<tr>
<td>ORAL</td>
<td>004673</td>
<td>Zegerid</td>
<td>omeprazole</td>
<td>Packet for solution: 20, 40mg</td>
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<td></td>
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<td>Capsules: 20, 40mg</td>
</tr>
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<td>Kapdex</td>
<td>Dexlansoprazole</td>
<td>Capsules, delayed-release: 30, 60mg</td>
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<td>ORAL</td>
<td>011590,</td>
<td>Protonix</td>
<td>pantoprazole</td>
<td>Tablets, delayed-release: 20 mg, 40 mg</td>
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<tr>
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<td>022008</td>
<td></td>
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<td>Suspension, delayed-release: 40mg</td>
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<td>pantoprazole</td>
<td>Tablets, delayed-release: 20 mg, 40 mg</td>
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<tr>
<td>ORAL</td>
<td>018847</td>
<td>Aciphex</td>
<td>rabeprazole</td>
<td>Tablets, delayed-release: 20 mg</td>
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</tbody>
</table>

Date: March 2014
<table>
<thead>
<tr>
<th>Approval Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>What is the diagnosis being treated?</strong></td>
</tr>
<tr>
<td>2. <strong>Is drug requested preferred?</strong></td>
</tr>
<tr>
<td>3. <strong>Will the prescriber consider a change to a preferred product?</strong></td>
</tr>
</tbody>
</table>
| 4. **Is diagnosis**  
 a) Zollinger-Ellison (251.5)?  
 b) Barrett’s esophagus (530.85)?  
 c) Multiple Endocrine Adenoma (237.4)?  
 d) Malignant Mastoma (202.6)?  
 e) MEN Type I (258.01)? | **Yes:** Approve for a life time; BID dosing OK.  | **No:** Go to 5 |
| 5. **Is the diagnosis dyspepsia (536.8)?** | **Yes:** Pass to RPH, DENY (OHP coverage) Diagnosis is below the line; preferred agents are available without PA.  | **No:** Go to 6 |
| 6. **Has patient tried and failed a preferred PPI for a 8 week trial (2 weeks for H. Pylori)?** | **Yes:** Go to #7  | **No:** Go to #12 |
| 7. **Is diagnosis H.Pylori?** | **Yes:** Approve for 2 weeks – BID dosing OK  | **No:** Go to #8 |
| 8. **Is diagnosis active GI bleed?**  
(531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2)  
and/or does patient have 2 or more of the following risk factors:  
- > 65 years  
- requires > 3 mths of NSAIDs, aspirin or steroids  
- on anticoagulation (warfarin, enoxaparin, etc.)  
- History of GI Bleed or Ulcer? | **Yes:** Approve for 8 weeks - BID dosing OK  | **No:** Go to #9 |
| 9. **Is diagnosis Gastric or Duodenal Ulcer**  
(531.3-531.9, 531.3-532.9, 533.3-533.9, 534.3-534.9)  
and/or does patient have 2 or more of the following risk factors:  
- > 65 years  
- requires > 3 mths of NSAIDs, aspirin or steroids  
- on anticoagulation (warfarin, enoxaparin, etc.)  
- History of GI Bleed or Ulcer? | **Yes:** Approve QD for 1 year, if previously failed an 8 week QD trial at highest dose approve BID for 1 year.  
May approve BID dosing for pediatrics <12 years old  | **No:** Go to #10 |
| 10. **Is the diagnosis symptomatic GERD**  
(530.81, 530.10 – 530.19)  
and/or does patient have 2 or more of the following risk factors:  
- > 65 years  
- requires > 3 mths of NSAIDs, aspirin or steroids  
- on anticoagulation (warfarin, enoxaparin, etc.)  
- History of GI Bleed or Ulcer? | **Yes:** Approve QD dosing for 1 year; if previously failed an 8 week QD trial at highest dose approve BID for 1 year.  
May approve BID dosing for pediatrics <12 years old  | **No:** Go to #11 |
| 11. **Is diagnosis**  
 a) Ulcer of esophagus (530.2x)  
 b) Stricture & stenosis of esophagus (530.3)  
 c) Perforation of esophagus (530.4)  
and/or does patient have 2 or more of the following risk factors:  
- > 65 years  
- requires > 3 mths of NSAIDs, aspirin or steroids  
- on anticoagulation (warfarin, enoxaparin, etc.)  
- History of GI Bleed or Ulcer? | **Yes:** Approve up to BID for 1 year.  | **No:** Go to #13 |
| 12. **Is the request for tube administration?** | Yes: Approve QD dosing for 1 year.  
May approve BID dosing for pediatrics <12 years old.  | **No:** Pass to RPH. Deny and recommend omeprazole 20 mg QD or BID. |
| 13. **All other diagnoses will need to be evaluated by a pharmacist for appropriateness and OHP line coverage.** | **Diagnoses above the line and where PPI is appropriate can be covered.**  
**Diagnoses below the line and where PPI is appropriate should be denied as not covered.**  
**Diagnoses above the line but where PPIs are not appropriate should be denied and not medically appropriate.** |
**Clinical Notes:**

**FDA safety alerts:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium difficile-associated diarrhea&lt;sup&gt;10&lt;/sup&gt;</td>
<td>PPIs may be associated with an increased risk of <em>Clostridium difficile</em>–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.</td>
</tr>
<tr>
<td>Low magnesium level associated with long-term PPI use&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Prescription PPIs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.</td>
</tr>
</tbody>
</table>
| Avoid concomitant use of Plavix<sup>®</sup> and omeprazole<sup>12</sup> | FDA issued a reminder that it **continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole** because the co-administration can result in significant reductions in clopidogrel’s active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature. Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. Omeprazole is found in prescription products (Prilosec, Zegerid, and generic products) and over-the-counter products (Prilosec OTC, Zegerid OTC, and generic products). FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals:  
  - With regard to the proton pump inhibitor (PPI) drug class, this recommendation **applies only to omeprazole** and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.  
  - Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole. |
Drug Class Review
Proton Pump Inhibitors

Preliminary Scan Report
December 2014

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
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Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director
Oregon Health & Science University

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the US Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

June 2013: Dexlansoprazole single drug addendum (searches through April 2013)
May 2009: Update Report #5 (searches through November 2008)

Date of Last Preliminary Update Scan Reports (since last full report update)

March 2010: Scan #1
November 2011: Scan #2
December 2012: Scan #3

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different PPIs in patients with symptoms of GERD?

2. What is the comparative effectiveness of different proton pump inhibitors in treating peptic ulcer and NSAID-induced ulcer?

3. What is the comparative effectiveness of different proton pump inhibitors in preventing ulcer in patients taking an NSAID?

4. What is the comparative effectiveness of different proton pump inhibitors in eradicating helicobacter pylori infection?

5. Is there evidence that one treatment strategy (e.g., stepping down to a lower dose, treatment as needed versus continuous treatment, high dose versus standard dose, or switching to an H2
antagonist), is more effective or safer than another for longer-term treatment (more than 8 weeks) in patients with GERD or ulcer?

6. What is the comparative safety and adverse events of different PPIs in patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer? 7. Are there subgroups of patients based on demographics, other medications, or co-morbidities (including patients with nasogastric tubes, or who cannot swallow solid oral medications) for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adults or children with symptoms of
- gastroesophageal reflux
- peptic ulcer (gastric or duodenal)
- NSAID-induced ulcer

Interventions

- Omeprazole (Prilosec®, Prilosec OTC®)
- Omeprazole/sodium bicarbonate (Zegerid®)
- Lansoprazole (Prevacid®)
- Pantoprazole (Protonix®)
- Rabeprazole (Aciphex®)
- Esomeprazole (Nexium®)

Effectiveness outcomes

- Symptoms
- Endoscopic healing
- Eradication rates
- Functional outcomes
- Quality of life

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events (e.g., diarrhea)

Study designs

- For comparative effectiveness of different PPIs, head-to-head randomized controlled trials comparing one PPI to another.
- For comparative safety of different PPIs, head-to-head randomized controlled trials or comparative observational studies.
• For comparative effectiveness and safety of different longer-term treatment strategies, randomized controlled trials with any comparison group.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from October 2012 through January 2014 including terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and boxed warnings. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), Veterans Affairs Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/), The Cochrane Collaboration (http://www.cochrane.org/reviews/index.htm), National Coordinating Center for Health Technology Assessment (NCCHTA) (http://www.ncchta.org/), and the NHS Centre for Reviews and Dissemination (CRD) (http://www.york.ac.uk/inst/crd/). All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

ACIPHEX® SprinkleTM (rabeprazole sodium) delayed-release capsules was approved in March 2013 for the following conditions

- Healing of erosive or ulcerative GERD in adults
- Maintenance of healing of erosive or ulcerative GERD in adults
- Treatment of symptomatic GERD in adults
- Healing of duodenal ulcers in adults
- Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence in adults
- Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome in adults
- Short-term Treatment of symptomatic GERD in adolescent patients 12 years of age and older treatment of GERD in pediatric patients 1 to 11 Years of Age
New drug identified in previous Preliminary Update Scan

Dexlansoprazole (Dexilant®; previously named Kapidex) was approved in January 2009. The EPC produced a single drug addendum on the new drug dexlansoprazole in June 2013. No other drugs were identified in the previous scans.

New Indications

New indications identified in this Preliminary Update Scan
None identified.

Identified in previous Preliminary Update Scans
June 2011: The indication for maintenance of healed erosive esophagitis for Dexilant® was expanded to include the relief of heartburn. The EPC produced a single drug addendum on the new drug dexlansoprazole in June 2013. No other new indications were identified in the previous scans.

New Boxed Warnings

Identified in this Preliminary Update Scan
None identified

Identified in previous Preliminary Update Scans
No new boxed warnings were included in the previous scans

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
A protocol of a Cochrane review “High dose versus standard dose proton pump inhibitor for short term management of erosive reflux oesophagitis” is available though it is not clear when the study will be completed. The protocol is available at http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010581/pdf.

Reviews identified in previous Preliminary Update Scans

Randomized Controlled Trials

Trials identified since the most recent Full Report
For this scan, Medline searches resulted in 91 citations. Of those, there was only 1 new head to head trial comparing esomeprazole to lansoprazole in patients with helicobacter pylori. Previous scans identified 6 head to head trials in 7 publications. Most of the trials were conducted in patients with GERD. Additionally, we found 2 long term trials (>8 weeks duration), one comparing omeprazole to H2RA antagonist ranitidine in children and the other compared standard to lower dose of rabeprazole in patients with upper GI symptoms. Characteristics of the relevant trials are included in tables 2 and 3 below and the abstracts are included in Appendix A.
Note that in the previous scan, there were 2 new trials reported in 1 publication on dextlansoprazole. Those two trials are not listed in the table below as they are already included in the single drug addendum report.

Table 1. New head-to-head trials of proton pump inhibitors*

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Comparison</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggleston, 2009</td>
<td>Esomeprazole vs rabeprazole</td>
<td>GERD</td>
</tr>
<tr>
<td>Hein, 2011</td>
<td>Pantoprazole magnesium vs pantoprazole sodium</td>
<td>GERD</td>
</tr>
<tr>
<td>Labenz, 2009a, 2009b</td>
<td>Esomeprazole vs pantoprazole</td>
<td>GERD (healing and maintenance)</td>
</tr>
<tr>
<td>Lee, 2010</td>
<td>Esomeprazole vs rabeprazole</td>
<td>Helicobacter pylori eradication in dyspepsia</td>
</tr>
<tr>
<td>Liu, 2013</td>
<td>Rabeprazole vs Lansoprazole</td>
<td>Helicobacter pylori eradication</td>
</tr>
<tr>
<td>Pace, 2011</td>
<td>Rabeprazole vs omeprazole</td>
<td>GERD, healing rate by BMI</td>
</tr>
<tr>
<td>Zheng, 2009</td>
<td>Esomeprazole vs Lansoprazole vs Pantoprazole vs Omeprazole</td>
<td>GERD symptoms</td>
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</table>

*Shading indicates trials identified in this preliminary update scan

Table 2. Other Trials

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<th>Focus</th>
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</thead>
<tbody>
<tr>
<td>Sanuki, 2012</td>
<td>Rabeprazole 10mg vs 20 mg</td>
<td>Upper GI symptoms</td>
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<tr>
<td>Umarino, 2012</td>
<td>Omeprazole vs ranitidine</td>
<td>GERD in children</td>
</tr>
</tbody>
</table>

*Shading indicates trials identified in this preliminary update scan
Appendix A. Abstracts of potentially relevant new trials of proton pump inhibitors (n=3)

This scan
Different types of proton pump inhibitor (PPI)-based triple therapies could result in different Helicobacter pylori eradication rates. This study aimed to compare the efficacy and safety of rabeprazole- and lansoprazole-based triple therapies in primary treatment of H. pylori infection. From September 2005 to July 2008, 426 H. pylori-infected patients were randomly assigned to receive a 7-day eradication therapy with either rabeprazole 20mg bid (RAC group, n=222) or lansoprazole 30mg bid (LAC group, n=228) in combination with amoxicillin 1g bid and clarithromycin 500mg bid. The patients received follow-up esophagogastroduodenoscopy (EGD) and/or (13)C-urea breath test 12-16 weeks later to define H. pylori status. Their personal and medical history, compliance and side effects were obtained by using a standardized questionnaire. Intention-to-treat analysis revealed that the eradication rate was 87.84% in the RAC group and 85.96% in the LAC group (p=0.56). All patients returned for assessment of compliance (100% in the LAC group vs. 99.50% in the RAC group; p=0.32) and adverse events (7.20% in the RAC group vs. 5.70% in the LAC group, p=0.51). Univariate analysis suggested that patients with nonsteroid anti-inflammatory agent (NSAID) use had lower eradication rates than those without (76.71% vs. 88.74%; p=0.006). Our results showed that efficacy and safety were similar in rabeprazole- and lansoprazole-based primary therapies. The influence of NSAID usage on H. pylori eradication needs to be further investigated. Copyright 2012. Published by Elsevier B.V.

BACKGROUND: Patients using low-dose aspirin (LDA) have an increased risk of gastroduodenal mucosal lesions and upper gastrointestinal symptoms. We aimed to clarify the efficacy of rabeprazole for preventing peptic ulcer, esophagitis, and gastrointestinal symptoms associated with LDA.
METHODS: Patients with a history of peptic ulcers who were receiving LDA for cardiovascular or cerebrovascular disease were randomly assigned to receive rabeprazole at 10 mg daily, rabeprazole at 20 mg daily, or gefarnate (a cytoprotective anti-ulcer agent) at 50 mg twice daily. The primary endpoint was the development of gastric and/or duodenal ulcer at 12 weeks. The modified Lanza score (MLS) and gastrointestinal symptoms were evaluated at baseline and at 12 weeks.
RESULTS: The full analysis set comprised 261 patients (rabeprazole 10 mg: n = 87, rabeprazole 20 mg: n = 89, gefarnate 100 mg: n = 85). The cumulative incidences of gastroduodenal ulcers at 12 weeks in the 10 mg rabeprazole group, 20 mg rabeprazole group, and gefarnate group were 7.4, 3.7, and 26.7 %, respectively (rabeprazole group 5.5 % vs. gefarnate group 26.7 %, hazard ratio [HR] 0.179; 95 % confidence interval [CI] 0.082-0.394; p < 0.0001). The proportions of patients with an MLS of >1 and erosive esophagitis were significantly lower in the rabeprazole group than in the gefarnate group at 12 weeks (gastric lesions 33.5 vs. 62.4 %, p < 0.0001; duodenal lesions 5.7 vs. 24.7 %, p < 0.0001; erosive esophagitis 5.8 vs. 19.4 %, p < 0.0001). Rabeprazole was significantly more effective than gefarnate for the resolution and prevention of gastrointestinal symptoms (resolution 53.6 vs. 25.0 %, p = 0.017; occurrence 9.2 vs. 28.3 %, p = 0.0026).
CONCLUSIONS: Rabeprazole is more effective than gefarnate for reducing the risk of recurrence of peptic ulcer, esophagitis, and gastrointestinal symptoms in LDA users.

The effect of antisecretory treatment on extraesophageal symptoms of gastroesophageal reflux disease was evaluated. Seventy-eight children presenting with typical and extraesophageal symptoms of gastroesophageal reflux disease underwent a multichannel intraluminal impedance and pH monitoring (MII/pH). Children with a positive MII/pH were randomly treated with proton pump inhibitors (PPIs) or histamine H(2) -receptor antagonists (H(2) RAs) during 3 months. At the end of the treatment period, all patients were recalled. A second treatment period of 3 months was given to those patients who were not symptom-free after 3 months. Thirty-five of the forty-one (85.4%) children with a pathologic MII/pH presented with extraesophageal symptoms and were treated with PPIs (omeprazole; n:19) or H(2) RAs (ranitidine; n:16) for 12 weeks. After 3 months, 11/19 (57.9%) PPI-treated patients had a complete resolution of symptoms; 6/8 nonresponders were treated with PPI for another 3 months and became all symptom-free. The other two underwent a Nissen fundoplication. Only 5/16 (31.2 %) patients treated with H(2) RAs had a complete resolution of symptoms after 3 months; 1/11 was treated again with H(2) RAs during 3 months, and 10/11 were changed to PPIs. In 3/10, a partial resolution of symptoms was achieved, while in 7/10, a complete remission was obtained (P < 0.05). Antisecretory reflux treatment improves extraesophageal reflux symptoms. The efficacy of PPIs is superior to that of H(2) RAs in these children. 2012 Copyright the Authors. Journal compilation 2012, Wiley Periodicals, Inc. and the International Society for Diseases of the Esophagus.

Identified in the previous Preliminary Update Scan (N=6 studies, 7 publications)


BACKGROUND: Proton pump inhibitors (PPIs) are well established as first-line agents for the treatment of moderate-to-severe gastro-oesophageal reflux disease (GORD). Although all PPIs heal oesophageal lesions and provide symptomatic relief, breakthrough symptoms may occur as acidity levels rebound. Pantoprazole magnesium (pantoprazole-Mg) has a longer elimination half-life than pantoprazole sodium (pantoprazole-Na), resulting in prolonged drug exposure.

OBJECTIVE: This study compares the clinical efficacy and safety of once-daily pantoprazole-Mg 40 mg with that of once-daily pantoprazole-Na 40 mg in the management of GORD. METHODS: This was a randomized, double-blind, controlled, multicentre study of non-inferiority design in outpatients with GORD. The study was conducted in 53 centres in Germany from 12 May 2003 to 18 September 2003. Male or female outpatients (aged >=18 years) with endoscopically confirmed GORD stage I-III (according to the Savary-Miller classification modified by Siewert) were enrolled. Using a computer-generated randomization list, patients were randomized to treatment with pantoprazole-Mg 40 mg plus placebo or pantoprazole-Na 40 mg plus placebo, both given once daily for 4 or 8 weeks depending on healing of oesophagitis. The primary objective was endoscopic healing at 8 weeks. RESULTS: The intent-to-treat (ITT) group consisted of 636 patients (322 receiving pantoprazole-Mg and 314 receiving pantoprazole-Na). Endoscopically confirmed healing of reflux oesophagitis after 8 weeks occurred in 87.3% (95% CI 83.1, 90.7) of patients receiving pantoprazole-Mg and 85.0% (95% CI 80.6, 88.8) of patients receiving pantoprazole-Na (ITT population). The lower bound of the 95% CI for the between-group treatment difference was -1.3, which was within the predefined margin of non-inferiority of -10% to 0%. Healing rates after 4 weeks were superior in the pantoprazole-Mg group (72.7% [95% CI...
compared with the pantoprazole-Na group (66.2% [95% CI 60.7, 71.5]), and the one-sided (lower bound) of the 95% CI for the difference between healing rates for the two treatments was within the predefined non-inferiority margin of -10% to 0%. Both treatments had a similar effect on GORD healing in subgroups of patients based on baseline oesophagitis grade and Helicobacter pylori status. Pantoprazole-Mg had similar efficacy to pantoprazole-Na in relieving a broad range of GORD-related symptoms across the course of the study, although symptomatic relief at 4 weeks was numerically higher in the pantoprazole-Mg group than in the pantoprazole-Na group (statistical analyses were not performed). Both treatments were well tolerated; most adverse events were of mild or moderate severity and unrelated to the study medication, and there were no unexpected safety concerns. CONCLUSION: Pantoprazole-Mg is clinically as effective and well tolerated as pantoprazole-Na in the treatment of GORD stages I-III, demonstrating non-inferiority for oesophageal healing at 8 weeks and superior healing rates at 4 weeks associated with high levels of symptomatic relief.


BACKGROUND: Increased BMI is associated with a higher risk of gastroesophageal reflux disease. AIMS: To investigate whether overweight/obesity (BMI>=25 kg/m(2)) affects rabeprazole clinical efficacy versus omeprazole in patients with erosive esophagitis (EE).

PATIENTS AND METHODS: Post-hoc analysis of EE healing rate and symptom response stratified by patient BMI was performed on data from a multicenter, double-blind, randomized, 4-to-8-week trial comparing EE healing with rabeprazole (20 mg daily) and omeprazole (20 mg daily). Analysis of variance, two-sample t-test, Blackwelder's test for equivalence, log-rank, and Cochran-Mantel-Haenszel tests were used to analyze comparisons. RESULTS: In the two BMI groups (<25 kg/m(2) and >=25 kg/m(2) respectively), rabeprazole and omeprazole were equally effective for mucosal healing regardless of patient's BMI (N=542, P>0.05). However, in overweight/obese patients, rabeprazole was significantly faster than omeprazole in inducing heartburn relief during the first treatment week (P<0.0001). CONCLUSIONS: Results of this study show that the clinical efficacy of rabeprazole is maintained in overweight/obese patients with gastroesophageal reflux disease and suggest that this subgroup of patients may derive, from rabeprazole, even greater benefit than lean patients.


BACKGROUND: A trial of empirical PPI therapy is usual practice for most patients with symptoms of gastro-oesophageal reflux disease (GERD) in primary care. AIM: To determine if the 4-week efficacy of rabeprazole 20 mg for resolving heartburn and regurgitation symptoms is non-inferior to esomeprazole 40 mg or 20 mg. METHODS: In all, 1392 patients were randomized to rabeprazole 20 mg, esomeprazole 20 mg or 40 mg once daily. Patients, doctors and assessors were blinded. Symptom resolution data were collected on days 0-7 and day-28 using the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index with a shortened version used on days 8-27. RESULTS: Rabeprazole 20 mg was non-inferior to esomeprazole 40 mg for complete resolution of regurgitation and satisfactory resolution of heartburn and regurgitation. For complete heartburn resolution, the efficacy of rabeprazole 20 mg and esomeprazole 40 mg was statistically indistinguishable, although the non-inferiority test was inconclusive. Rabeprazole 20 mg was non-inferior to esomeprazole 20 mg for all outcomes. CONCLUSIONS: In uninvestigated GERD patients, rabeprazole 20 mg was non-inferior to esomeprazole 40 mg for complete and satisfactory relief of regurgitation and satisfactory relief of heartburn, and not different for complete resolution of heartburn.

BACKGROUND: Ability to predict freedom from heartburn relapse during maintenance therapy for healed reflux oesophagitis may facilitate optimal treatment choices for individual patients.
AIM: To determine factors predicting freedom from heartburn relapse during maintenance proton pump inhibitor therapy in patients with healed reflux oesophagitis.
METHODS: This post-hoc analysis used data from the maintenance phase of the EXPO study (AstraZeneca study code: SH-NEG-0008); 2766 patients with healed reflux oesophagitis and resolved heartburn received once-daily esomeprazole 20 mg or pantoprazole 20 mg for 6 months. Multiple logistic regression analysis determined factors associated with freedom from heartburn relapse.
RESULTS: Heartburn relapse rates were lower with esomeprazole than pantoprazole in all subgroups analysed. Esomeprazole treatment was the factor most strongly associated with freedom from heartburn relapse (odds ratio 2.08; P < 0.0001). Other factors significantly associated with freedom from heartburn relapse were Helicobacter pylori infection, greater age, non-obesity, absence of epigastric pain at baseline, pre-treatment nonsevere heartburn and GERD symptom duration < or =5 years.
CONCLUSIONS: Several factors predict freedom from heartburn relapse during maintenance proton pump inhibitor therapy for healed reflux oesophagitis, the strongest being choice of proton pump inhibitor. These findings outline the importance of optimizing acid control and identifying predictors of relapse for effective long-term symptom management in reflux oesophagitis patients.


BACKGROUND: The ability to predict symptom response to reflux oesophagitis-healing therapy may optimize treatment decisions.
AIM: To identify factors associated with heartburn resolution in patients receiving acid-suppressive therapy for reflux oesophagitis.
METHODS: In this multicentre, randomized, double-blind trial (EXPO; AstraZeneca study code: SH-NEG-0008), patients with endoscopically confirmed reflux oesophagitis and reflux symptoms received once-daily proton pump inhibitor therapy [esomeprazole 40 mg (n = 1562) or pantoprazole 40 mg (n = 1589)] for >or=4 weeks. Factors associated with heartburn resolution after 4 weeks were identified by multiple logistic regression analysis.
RESULTS: Esomeprazole therapy, positive Helicobacter pylori status and greater age were associated with an increased likelihood of heartburn resolution [odds ratio (95% confidence interval): 1.31 (1.12, 1.54), 1.44 (1.19, 1.74) and 1.013 (1.007, 1.019) per year, respectively; all P < 0.001]. Men and patients with no acid regurgitation or epigastric pain pre-treatment were also more likely to achieve heartburn resolution (all P < 0.05).
CONCLUSIONS: The use of esomeprazole rather than pantoprazole increases the probability of achieving resolution of heartburn during reflux oesophagitis-healing therapy. Other factors, including H. pylori status, age, gender and symptom profile may be helpful in determining the likelihood of heartburn resolution in such patients.


OBJECTIVE: Our study aimed to assess the effectiveness of esomeprazole or rabeprazole in combination with amoxicillin and clarithromycin for the eradication of Helicobacter pylori in Hong Kong non-ulcer dyspepsia (NUD) patients. METHODS: A prospective clinical trial was conducted at the Alice Ho Miu ling Nethersole Hospital outpatient endoscopy center from June 2004 to December 2005. Participants received amoxicillin 1 g, clarithromycin 500 mg, and,
esomeprazole 20 mg (EAC) or rabeprazole 20 mg (RAC), all given twice daily for 1 week. The H. pylori status was determined by the [13C] urea breath test at least 4 weeks after completion of the treatment. Mutation status of CYP2C19 in exon 4 and exon 5 associated with the poor metabolizer phenotype was determined. RESULTS: The intention-to-treat eradication rates in patients treated with RAC and EAC were 77% and 84.6% respectively, and per protocol-based eradication rates were 83.7% and 88.9% respectively. The eradication rates did not vary with CYP2C19 phenotype found. For clarithromycin-sensitive strains, the cure rates were statistically significant regardless of CYP2C19 polymorphism (P < 0.0001). CONCLUSION: Triple therapy with either EAC or RAC is effective for Hong Kong Chinese NUD patients with H. pylori infection. Success eradication was related to clarithromycin resistance and not CYP2C19 genotype.


AIM: To clarify whether there is any difference in the symptom relief in patients with reflux esophagitis following the administration of four Proton pump inhibitors (PPIs). METHODS: Two hundred and seventy-four patients with erosive reflux esophagitis were randomized to receive 8 wk of 20 mg omeprazole (n = 68), 30 mg of lansoprazole (n = 69), 40 mg of pantoprazole (n = 69), 40 mg of esomeprazole (n = 68) once a day in the morning. Daily changes in heartburn and acid reflux symptoms in the first 7 d of administration were assessed using a six-point scale (0: none; 1: mild; 2: mild-moderate; 3: moderate; 4: moderate-severe; 5: severe). RESULTS: The mean heartburn score in patients treated with esomeprazole more rapidly decreased than those receiving other PPI. Complete resolution of heartburn was also more rapid in patients treated with esomeprazole for 5 d compared with omeprazole (P = 0.0018, P = 0.0098, P = 0.0027, P = 0.0137, P = 0.0069, respectively), lansoprazole (P = 0.0020, P = 0.0046, P = 0.0037, P = 0.0016, P = 0.0076, respectively), and pantoprazole (P = 0.0006, P = 0.0005, P = 0.0009, P = 0.0031, P = 0.0119, respectively). There were no significant differences between the four groups in the rate of endoscopic healing of reflux esophagitis at week 8. CONCLUSION: Esomeprazole may be more effective than omeprazole, lansoprazole, and pantoprazole for the rapid relief of heartburn symptoms and acid reflux symptoms in patients with reflux esophagitis.
Month/Year of Review: March 2014  
Date of Last Review: November 2012

PDL Classes: GI – Digestive Enzymes  
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: CREON®, LIPASE/PROTEASE/AMYLASE
- Nonpreferred Agents: PANCREZE®, PERTZYE®, PANCRELIPASE®, ULTRESA®, VIOKASE®, ZENPEP®

Previous Conclusions and Recommendations:
- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects. Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzyme replacement products (PEPs) in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change in CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).4,5
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which can potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Other side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.
- Due to no apparent differences in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration concerns.

Conclusions and Recommendations:
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCT’s) comparing PEP’s to placebo or other products was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
None
New Trials (Appendix 1):
A total of 43 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

A 51-week, open-label extension clinical trial in India assessed the efficacy and safety of pancreatin (Creon) 40000 in patients with pancreatic exocrine insufficiency due to chronic pancreatitis.\(^1\) Compared to placebo, statistically significant improvements from baseline to end of the extension in mean coefficient of fat absorption, coefficient of nitrogen absorption, stool fat, stool nitrogen, and stool weight were observed. Significant improvements in both mean body weight and BMI were also observed.\(^1\)

A 1 week, double-blind, randomized, placebo-controlled study compared Creon 25000 minimicrospheres to placebo in treating pancreatic exocrine insufficiency after pancreatic resection.\(^2\) The primary efficacy measure was change in coefficient of fat absorption. The change in the Creon group increased and decreased in the placebo group, with a statistically significant treatment difference of 32.6% (95% CI 19.9-45.4; p<0.001). Stool frequency decreased by 0.9 stools/day in the Creon group and increased by 0.5 stools/day in the placebo group. Statistically significant improvements from baseline were also seen in body weight and body mass index. Adverse events occurred more in the treatment group than placebo (37.5% vs. 26.9%) and flatulence was the most common. There were no adverse events leading to discontinuations.
References:

Appendix 1: Abstracts of RCTs:

1. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minicapsules in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013 Mar-Apr;13(2):133-9

**BACKGROUND/OBJECTIVES:**
To assess the efficacy and safety of pancreatin (pancrelipase) enteric-coated minicapsules (MMS) over a one-year period in patients with pancreatic exocrine insufficiency (PEI) due to chronic pancreatitis (CP).

**METHODS:**
This was a 51-week, open-label extension (OLE) of a one-week, multicenter, double-blind, randomized, placebo-controlled trial in India that enrolled patients ≥18 years of age with confirmed PEI due to CP. Patients received pancreatin (Creon® 40000 MMS™) at a dose of 80,000 Ph. Eur. lipase units with each of three main meals/day and 40,000 with each of up to three snacks/day.

**RESULTS:**
Of 61 patients entering the OLE, 48 completed treatment (nine were lost to follow up, two withdrew consent, one discontinued due to adverse event [acute exacerbation of CP], one protocol violation). There were significant improvements from baseline to end of OLE in mean ± SD coefficient of fat absorption (CFA: 22.7 ± 12.2%), coefficient of nitrogen absorption (CNA: 6.5 ± 7.9%), body weight (4.9 ± 4.9 kg), BMI (1.9 ± 1.9 kg/m²), and most nutritional laboratory parameters tested (p ≤ 0.001). Mean daily stool frequency was reduced from 2.8 to 1.6 (p < 0.001). Improvements in clinical symptoms, clinical global impression of disease symptoms, and quality of life were also observed. Treatment-emergent adverse events (TEAEs) were observed in 64% of patients overall. Only 13% of patients experienced TEAEs judged treatment related.

**CONCLUSIONS:**
In patients with PEI due to CP, treatment with pancreatin for one year was associated with significant improvements in fat absorption, nitrogen absorption, and nutritional parameters, improvements in clinical symptoms, and a favorable safety and tolerability profile.

2. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minicapsules (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. Aliment Pharmacol Ther. 2013 Apr;37(7):691-702

**BACKGROUND:**
Pancreatic exocrine insufficiency (PEI) often occurs following pancreatic surgery.

**AIM:**
To demonstrate the superior efficacy of pancreatin 25 000 minicapsules (Creon 25000 MMS; 9-15 capsules/day) over placebo in treating PEI after pancreatic resection.

**METHODS:**
A 1-week, double-blind, randomised, placebo-controlled, parallel-group, multicentre study with a 1-year, open-label extension (OLE). Subjects ≥18 years old with PEI after pancreatic resection, defined as baseline coefficient of fat absorption (CFA) <80%, were randomised to oral pancreatin or placebo (9-15 capsules/day: 3 with main meals, 2 with snacks). In the OLE, all subjects received pancreatin. The primary efficacy measure was least squares mean CFA change from baseline to end of double-blind treatment (ancova).

**RESULTS:**
All 58 subjects randomised (32 pancreatin, 26 placebo) completed double-blind treatment and entered the OLE; 51 completed the OLE. The least squares mean CFA change in the double-blind phase was significantly greater with pancreatin vs. placebo: 21.4% (95% CI: 13.7, 29.2) vs. -4.2% (-12.8, 4.5); difference 25.6% (13.9, 37.3), P < 0.001. The mean ± s.d. CFA increased from 53.6 ± 20.6% at baseline to 78.4 ± 20.7% at OLE end (P < 0.001). Treatment-emergent adverse events occurred in 37.5% subjects on pancreatin and 26.9% on placebo during double-blind treatment, with flatulence being the most common (pancreatin 12.5%, placebo 7.7%). Only two subjects discontinued due to treatment-emergent adverse events, both during the OLE.

**CONCLUSIONS:**
This study demonstrates superior efficacy of pancreatin 25 000 over placebo in patients with PEI after pancreatic surgery, measured by change in CFA. Pancreatin was generally well tolerated at the high dose administered.